



BRAIN
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Brain

A Journal of Neurology

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BRAIN.

PART 1, VOL. 57.

THE GREAT VEIN OF GALEN AND THE SYNDROME OF INCREASED INTRACRANIAL PRESSURE.

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(From the Department of Pharmacology, Manchester University.)

THIS inquiry constitutes an attempt to examine the data on which is based the theory that interference with the flow of blood through the great vein of Galen may bring about a state of increased intracranial pressure. Since Stopford [24] advanced the view that the increased intracranial pressure which accompanies cerebral tumour is frequently a consequence of an obstruction to the flow of blood through this vein, the subject has become one of the greatest importance. The evidence that obstruction to the great vein of Galen may bring about a state of increased intracranial pressure has been drawn from three different sources: (1) The post-mortem finding of a communicating hydrocephalus in cases of thrombosis of the great vein of Galen or of the straight sinus and in which no other cause can be assigned for the hydrocephalus; (2) the experiments of Dandy and Blackfan [6] on the effect of occlusion of the great vein of Galen in dogs; (3) certain deductions based on a consideration of the anatomy of the great vein of Galen and of the relative incidence of hydrocephalus in cases of cerebral tumours localized in different parts of the brain.

THE FORMATION OF THE CEREBROSPINAL FLUID.

Before proceeding to a detailed examination of the evidence derived from these different sources, it is proposed to consider very briefly the manner of formation and absorption of the cerebrospinal fluid. The cerebrospinal fluid is formed mainly by the choroid plexuses of the lateral ventricles and to a less extent by those of the third and fourth

ventricles. Although there is considerable evidence in favour of the view that the fluid is formed by a simple filtration and not by vital secretion (Mestrezat [19]), complete proof is lacking and the subject awaits further investigation. In this connection it is important to note that those who maintain that an increased production of cerebrospinal fluid follows obstruction to the venous outflow from the choroid plexuses are almost compelled to accept the theory of simple filtration, for it is unlikely that an increased secretion, which is a vital process, could be induced by venous obstruction. If, for the time being, we accept the theory of filtration, it becomes apparent that the amount of fluid formed over a given period will be determined by two main factors: (1) The height of the choroidal capillary pressure; (2) the capillary circulation rate. Total obstruction to the entire venous return of the plexuses, although raising the capillary pressure, would soon be followed by concentration of the non-filtrable constituents of the blood, cessation of filtration and infarction of the organs. On the other hand an intermittent or incomplete obstruction might raise the capillary pressure without seriously diminishing the rate of flow through the capillaries, and under these circumstances filtration could proceed unchecked and might be increased.

THE ABSORPTION OF CEREBROSPINAL FLUID.

The evidence regarding the method by which the cerebrospinal fluid is absorbed is highly conflicting. Two main schools of thought exist. Weed [25], as a result of experiments based on the original investigations of Key and Retzius [17], believes that the cerebrospinal fluid is absorbed mainly through the Pacchionian granulations or "arachnoid villi" into the cerebral venous sinuses and to a very slight extent into the lymphatic system. Confirmatory evidence has been supplied by Dixon and Halliburton [10], and by Frazier and Peet [12], and this would seem to be the favoured theory. On the other hand Dandy and Blackfan [6], as a result of experiments based largely on the excretion by the kidneys of diffusible dyes after their introduction into the subarachnoid space, conclude that the absorption of cerebrospinal fluid is a "diffuse process from the entire subarachnoid space," and that the fluid finds its way directly into the capillaries there. Still more recently Dandy [8] has provided further experimental evidence in favour of this theory. Although a detailed discussion of the phenomenon of the absorption of the cerebrospinal fluid would be out of place here, it is important to realize that on the basis of either theory an excessive formation

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of fluid need not of itself give rise to a state of increased intracranial pressure. This can occur (1) if the fluid is formed at a greater rate than that at which the absorption mechanism can deal with it, or (2) if it is formed in such quantities that the channels which normally drain it away become functionally too small to prevent its accumulation within the ventricles. As regards the first possibility Cushing [5] believes that a blocking of the arachnoid villi by extravasated blood-cells or products of inflammation may be an important cause of idiopathic hydrocephalus. There is, however, no evidence that the absorption mechanism normally is ever unable to deal with the maximum amount of fluid that the plexuses are capable of producing. As regards the second possibility, Dandy [7] has brought forward evidence that an obstruction to a main conducting channel, which need not always be complete, may be followed by hydrocephalus. Stopford [24], however, in order to account for the relatively slight distension of the fourth ventricle as compared with that of the lateral and the third ventricles in certain cases of hydrocephalus associated with cerebral tumours in which there has been no apparent obstruction of the aqueduct, considers that owing to obstruction of the great vein of Galen, "the production of fluid by the choroid plexuses is so great that only a proportion of it can be drained off along the aqueduct; consequently the pressure in these cavities (the lateral and the third ventricles) rapidly rises and dilatation results." To sum up, it would appear on purely theoretical grounds that obstruction to the great vein of Galen may, under certain circumstances, lead to an increased production of cerebrospinal fluid. An excessive production of cerebrospinal fluid need not of itself bring about a state of increased intracranial pressure. Such might occur in the special circumstances in which conduction or absorption is inadequate. We are now in a position to examine the data on which is based the theory that obstruction to the great vein of Galen causes increased intracranial pressure

(1) *Hydrocephalus following Thrombosis of the Great Vein of Galen or of the Straight Sinus.*

Dandy [7] has reviewed the literature relating to the finding at autopsy of hydrocephalus in cases of thrombosis of the great vein of Galen or of the straight sinus. In his paper, which appeared in 1919, he states: "The authentic cases in which thrombosis of the vein of Galen or straight sinus has caused hydrocephalus are few but apparently

definite. Newman (1882) reports a case, and Browning (1887) another." A careful search through the literature subsequently to Dandy's paper has failed to trace any further cases. It would appear, therefore, that since 1887 no case has been recorded in which hydrocephalus may have been brought about by thrombosis of the great vein of Galen or of the straight sinus. As the authenticity of the cases reported by Newman and Browning has so far never been disputed, and in view of the importance attached to them by Dandy and by most subsequent writers, it is proposed to consider each in detail.

The subject of Browning's excellent paper [4] was a girl, aged 6, who died in coma after an illness of three months. The symptoms were vague and indefinite. Autopsy revealed a dilatation of both lateral chambers, of the third and fourth ventricles and of the connecting iter; the straight sinus contained an organizing thrombus which, if not entirely blocking its lumen, very nearly did so. The thrombosis was the end-result of a perisinusitis of long standing. It will be observed that so far the case is beyond criticism. When, however, Browning came to examine the superior longitudinal sinus he found that although its lumen was everywhere free from antemortem clot, the walls of the sinus itself were involved in a perisinusitis similar to that affecting the straight sinus but which on naked-eye examination did not appear to be of as long standing as that of the latter. The lacunæ laterales were especially affected and seemed for the greater part to have been reduced to fibrous cords. Unfortunately Browning made no histological investigations and thus we lack more precise details of the extent and relative duration of the lesions and also of the condition of the subarachnoid space generally. There is, however, sufficient evidence that the arachnoid villi were seriously damaged, a finding which according to Weed [25] and to Cushing [5] may have accounted for the hydrocephalus. Thus the case is by no means free from complications and cannot therefore be admitted as an example of hydrocephalus following thrombosis of the straight sinus.

Newman's paper [20] unfortunately lacks the wealth of detail which is to be found in Browning's. The patient was a man, aged 55, who died in coma after an illness of about three months' duration. In vagueness of symptoms the case somewhat resembled the previous one. At autopsy the lateral ventricles were found to be considerably dilated and each contained an accumulation of about $4\frac{1}{2}$ oz. of clear straw-coloured fluid which on examination was found to contain 0.09 per cent. of "albuminous matter"; microscopical examination of the sediment

revealed a "few leucocytes and one or two crystals of cholesterine and margarine." The choroid plexuses were unusually vascular and there was a small whitish adherent clot at the point where the great vein of Galen and the inferior longitudinal sinus unite to form the straight sinus. None of the other vessels or sinuses contained clot. Unfortunately Newman failed to record the condition of the remaining ventricles and of the aqueduct. It is impossible, therefore, to be certain that the case was one of communicating hydrocephalus. The presence within the ventricles of a straw-colour fluid of relatively high albumin content and containing a few leucocytes would seem to suggest that the hydrocephalus had followed meningitis (Levinson [18]). However, in the absence of essential details it is impossible to determine its true nature.

It would appear, therefore, that an authentic case in which hydrocephalus has resulted from thrombosis of the great vein of Galen or of the straight sinus has so far not been recorded. On the other hand there appears to be definite evidence that thrombosis of the straight sinus and of the great vein of Galen can occur without the development of hydrocephalus. A case is recorded in St. George's Hospital Reports [21] of an anæmic girl, aged 20, in which a thrombosis of the straight sinus and of the great vein of Galen was discovered at autopsy. The clot is described as being "firm and of red colour mottled with white." The ventricles contained no excess of fluid and there were no additional lesions of note. It must be admitted, however, that it is difficult to form an estimate of the probable duration of the lesion.

(2) *Experimental Occlusion of the Great Vein of Galen.*

In a series of ten dogs, Dandy and Blackfan [6] occluded the great vein of Galen and the straight sinus at different points. The animals were kept alive for three to three and a half months. When they were killed it was discovered that hydrocephalus had developed in one instance only. The hydrocephalus was communicating in type and only moderate in degree; it was found in this particular case that the vein had been obstructed close to its point of origin. In the remaining nine cases the ventricles remained unaltered in size. From this single positive result and without any further attempt at confirmation, Dandy and Blackfan concluded that hydrocephalus occurs when the great vein of Galen is obstructed near its origin, and this view has obtained almost universal acceptance. Brain and Strauss, in "Recent Advances in Neurology" (1929), state, "Dandy has shown experimentally that hydrocephalus follows ligation of the great vein of Galen which drains the choroid

plexus, if the ligature be placed at its origin." Stopford, in a paper which appeared in 1926, expresses the opinion that Dandy has provided "convincing experimental evidence" that compression of the great vein of Galen causes an increased production of cerebrospinal fluid, and he states further that "Dandy has recently proved that occlusion of the great vein of Galen in dogs, provided it occurs at the origin of the vein and the development of a collateral circulation is thus prevented, causes internal hydrocephalus on account of the over-production of cerebrospinal fluid."

In order to verify Dandy and Blackfan's pronouncement that experimental obstruction of the great vein of Galen in dogs may be followed by hydrocephalus, this vein has been obstructed at various points along its course in 47 animals. None of these developed hydrocephalus. Thirteen animals died within three weeks as a direct or indirect consequence of operation, while six others, owing to the onset of distemper or of some other diseased condition, had to be destroyed before they had survived Dandy's prescribed period of three months. We are thus left with 28 cases in which the great vein of Galen was successfully obstructed and the animals maintained in good health until they were killed three or four months later. When the brains of these 28 animals were examined it was found that the vein had been obstructed at its origin in 13 instances and comparatively near its origin in 5 others. These cases are especially important, for, as already stated, Dandy and Blackfan believe that hydrocephalus occurs when an obstruction is placed at the origin of the great vein of Galen. Before proceeding to a more detailed consideration of these cases it is proposed to give an account of the operation which was employed in order to occlude the vein and of the methods used to examine the brains after death.

THE OPERATION.

With the exception of one important detail Dandy and Blackfan's technique has been followed as far as their brief account of their method of operation allows. Most breeds of dogs except the very large and heavy types were probably represented. The bulk of the animals, however, were mongrels. Short-haired terriers or small short-haired mongrels were the dogs of choice. The animals varied in age from six months upwards. Dogs under one year were found to be especially liable to develop distemper and when possible were avoided. The most suitable age seemed to lie between one and three years. The anæsthetic employed was morphia and intravenous chloralose.

The cranium is exposed by an ear to ear incision through the shaved scalp. Dandy and Blackfan seem to have worked through a plain opening in the vault of the skull situated over the posterior part of the corpus callosum. They do not indicate that they took any steps to close this opening. All their animals were probably left therefore with a comparatively large aperture in the cranium through which the cerebrospinal fluid may have drained and thus prevented the development of a state of increased intracranial pressure. In order to remedy this defect and to provide a skull which might be expected to function in the manner of a normal cranium, it was decided, after having performed a number of successful operations through an ordinary trephine hole, to open the cranium by turning down an osteoplastic flap. This was accomplished by making a bevelled half trephine cut through the bone over the superior longitudinal sinus and extending the ends downwards by means of bevelled saw cuts. With a little practice it was found possible to cut through the whole thickness of the bone without injuring the underlying dura. The flap was raised in the ordinary way. Care was taken that a piece of temporal muscle remained attached to its base. This is the only important modification made in Dandy and Blackfan's technique. By employing this method of opening the cranium a more convenient and more extensive exposure of the brain is obtained than is provided by a simple trephine hole; the flap, when correctly cut, returns perfectly into position and on killing the animal three months later careful inspection is required in order to determine on which side the cranium has been opened. The flap during operation is protected with saline gauze; the dura is freely opened in a cruciate manner close up to the superior longitudinal sinus which is retracted and the space between the cerebral hemispheres displayed. A retractor is then passed down between the hemispheres and with the aid of a head lamp and suction apparatus the inferior longitudinal vein lying on the corpus callosum and the great vein of Galen as it emerges from under cover of the splenium, are soon brought to light. In separating the hemispheres, veins are frequently torn across and for a time bleed freely. This can always be controlled by the application of hot saline. Bleeding from the superior longitudinal sinus, which occasionally is unavoidably injured in the cutting of the flap and is a more formidable complication, can usually be controlled by the application of a fascial graft. In order to expose the point where the veins of Galen unite to form the great vein of Galen it is necessary to divide the splenium of the corpus callosum. This is best accomplished with the aid of some blunt

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instrument such as a small aneurysm needle which has been partly straightened. The great vein of Galen is then exposed to view over its entire course, but before it can be taken up with a hook it has to be dissected out from its bed in the velum interpositum. In effecting this, small branches may be torn and for a time there may be slight bleeding which however soon subsides either of its own accord or with the help of hot saline. The vein is now seized with a small blunt hook and a silver clip placed and closed on the desired part of its course. The clips and clip holder were modelled on those used by Dandy and Blackfan and described in their original paper. The clip in position, the hemispheres are allowed to come together and the flap replaced. No attempt is made to suture the dura which at post-mortem examination is found to be entirely re-formed and often only slightly adherent to the cerebrum. The flap does not require to be fixed with sutures but will retain itself in position. A subcutaneous drain is inserted and the skin wound closed with interrupted silkworm sutures.

TREATMENT AFTER OPERATION.

The animals suffered surprisingly little discomfort after operation and by the next day were usually on their feet taking food. Sepsis was not found to be a serious complication and if it occurred at all never extended beyond the skin. Normally the wound was completely healed by the tenth or the fourteenth day. Pneumonia accounted for most deaths within the first three weeks and seemed frequently to occur as a complication of acute distemper. Immediately after operation radiograms were taken to determine if the flap fitted accurately and also to obtain some notion of the position of the clip. This was again repeated on the severed head. As this method of investigation provided no information which could not be obtained with greater accuracy by a direct examination of the cranium and brain after death it was later abandoned. A careful watch was maintained in order to discover if the animals developed symptoms which might be related to the onset of a state of increased intracranial pressure and from time to time the fundi were examined ophthalmoscopically for papilloedema. Apart from the occurrence in a few cases of diseases to which dogs in general are subject, the animals remained normal in every respect and ophthalmoscopic examination never revealed any trace of papilloedema. After a period varying from three to six months the animals were killed by decapitation.

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METHODS EMPLOYED FOR THE EXAMINATION OF THE BRAIN AFTER DEATH.

The severed head was treated in one of the following ways:—

(1) After a careful examination of the osteoplastic flap and underlying dura, the vault of the skull was removed and the entire head placed for fixation in 5 per cent. formol saline. Care was taken not to distort the brain. In order to achieve this the dura was opened only after some degree of fixation had been effected. After three days the brain was removed from the skull, entirely freed from its coverings and allowed to fix for another fortnight. A transverse vertical section was then made through the whole brain somewhat posterior to a point situated midway between the frontal and occipital poles and the size of the lateral and third ventricles and of the aqueduct observed. The exact position of the clip was determined either by a lateral dissection and piecemeal removal of the posterior portion of one cerebral hemisphere, or by a piecemeal removal from above downwards of the upper portion of the cerebral hemispheres and the corpus callosum until the great vein of Galen and its branches were displayed in their entirety. The clip was found always to be enclosed in a fibrous capsule which also involved the vein for a variable distance in front and behind. The amount of obliteration was ascertained with accuracy by passing a fine blunt probe into and along the vein until the obstruction was reached and then by opening up the vessel with a pair of fine scissors.

(2) Immediately after killing, cannulae were placed in both carotid arteries and the severed head perfused with normal saline until the vessels were washed clean of blood. After perfusion, the vault of the skull was removed and the termination of the great vein of Galen and the straight sinus displayed by cutting away part of the cerebral hemispheres. A small cannula was then introduced into the straight sinus and the great vein of Galen with its tributaries injected with carmine gelatine. The whole brain was then placed in formol saline for hardening. By this method it was possible to demonstrate very clearly the communications of the basilar vein with the veins of the base of the brain, and also the way in which collateral circulation was developed after occlusion of the anterior part of the great vein of Galen. Owing, however, to the deeply seated and relatively inaccessible position of the structures it was desired to inject and to the softness of unfixed brain substance this method was found to be difficult to apply, and success was not always achieved. Finally it was discarded in favour

of a method by which the whole head, after perfusion with normal saline through the carotid arteries, was injected through the external jugular veins with the gelatine mass. The brain was then fixed in the ordinary way. Besides abolishing the necessity of disturbing and distorting the brain before fixation this method was found to be entirely satisfactory for determining the extent and manner of formation of collateral circulation in relation to the occluded vessel. In later experiments this became the method of choice. It was also found possible to fill the veins by introducing the injection mass through the carotid arteries. At one time it was thought that the injection of fluid under pressure through the carotid arteries may possibly modify the size of the ventricular chambers. Experiments were accordingly conducted on normal heads with this in view when it was discovered that the injection of isotonic saline or of gelatine masses failed to modify to any appreciable extent the size of the ventricles.

(3) The head was perfused with normal saline followed by 5 per cent. formol saline and allowed to stand for a few hours, when the brain was removed and placed for further fixation in formol saline. The employment of this method was found essential when the choroid plexuses were required for histological purposes.

THE ANATOMY OF THE GREAT VEIN OF GALEN IN THE DOG.

In order to obtain a proper understanding of the effects which might reasonably be expected to follow obstruction at various points in the course of the great vein of Galen, it is necessary to possess a knowledge of the anatomy of the vein and of its main branches. A careful search through the relevant literature has failed to reveal a single account which contains the necessary details. Ellenberger and Baum [11] and Bradley [2], describe only the anatomy of the main trunk. Owing to the kindness of a colleague, the heads of a large number of normal dogs have been available, and these have been utilized for the purpose of a more detailed study of the vein and its tributaries. At an early stage in the investigation it was discovered that both the vein itself and its tributaries are subject to marked variations, and the account which follows may be regarded as a description of the average finding. Fig. 2 is a drawing from a brain which has been injected with a carmine-gelatine mass. The upper part of each cerebral hemisphere and the corpus callosum have been removed and the great vein of Galen with its tributaries exposed. It will be observed that in the dog the great vein of Galen is formed in the anterior part of the velum interpositum by the union of

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two relatively short veins of Galen and terminates at the anterior border of the tentorium cerebelli where it becomes the straight sinus. The two veins of Galen are themselves formed at a point close to the foramen of Monro by the union of the vein of the corpus striatum and the vein of the choroid plexus. The relatively short course of the veins of Galen and the long course of the great vein of Galen as compared with their

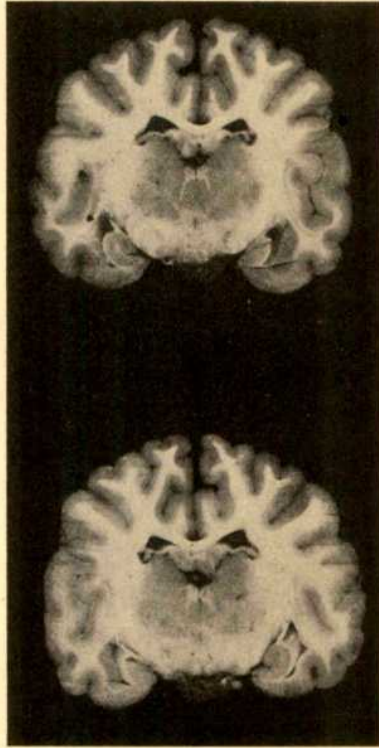


FIG. 1.—Transverse section through the brain of a greyhound in which the posterior part of the great vein of Galen has been occluded for five months. The section has been made anterior to the clip. The ventricles are normal in size.

condition in the human subject are noteworthy. The vein of the corpus striatum is small and very tortuous. It lies in a groove between the optic thalamus and the corpus striatum from which structures it derives most of its blood. The vein of Galen receives tributaries from the choroid plexuses of the lateral ventricles and also communicates with the striate and thalamic branches of the basilar vein. One large tributary which joins the vein of Galen shortly before it unites with its fellow is worthy of special note. In size it exceeds the vein of the corpus striatum;

it drains blood mainly from the optic thalamus but it also receives blood from the choroid plexus of the third ventricle and posteriorly it is in communication with the striate and thalamic branches of the basilar vein and with the veins at the base of the brain. This vessel plays an important part in establishing collateral circulation after occlusion of the great vein of Galen. The vein of Galen is joined at the point where it unites with its fellow of the opposite side to form the great vein of Galen by a number of small but fairly constant vessels from the septum lucidum.

The first tributaries to be received by the great vein of Galen are a number of small venules from the choroid plexus of the third ventricles. Occasionally these venules are united to form a common trunk which seldom attains a size of importance. As often as not, however, they are represented by a leash of venules. Usually a pair of rather stout tributaries is received from the side of the optic thalamus. These vessels, which join the vein of Galen on its under surface, are similarly sometimes represented by a leash of venules. As the great vein of Galen is about to emerge from under cover of the splenium of the corpus callosum it is joined by a pair of veins of moderate size. As these vessels correspond in their position and in the tributaries from which they receive blood to the basilar veins in the terminal part of their course in the human subject, it is proposed to refer to them as the "basilar veins."

It is convenient for the purposes of description to speak of that portion of the great vein of Galen which lies anterior to the point where it is joined by the basilar veins as the anterior part of the great vein of Galen and the portion which lies posterior to this point as the posterior part of the great vein of Galen. Although the point of termination of the basilar veins may vary, this method of describing the great vein of Galen is found to be useful when considering the effect of occluding it at different situations on its course.

Before proceeding to a description of the basilar vein and its communications it is necessary to consider the mode of termination of the veins at the base of the brain. It is noteworthy that in the dog the arrangement of the veins at the base of the brain differs markedly from that found in the human subject. The anterior cerebral vein is a relatively large vessel which drains blood mainly from the under surface of the frontal lobe. It is joined in the region of the anterior perforated spot by a number of veins from the island of Reil and the neighbouring structures. The common trunk so formed does not, however, course round the mid-brain as the basilar vein but passes along the lateral

aspect of the mid-brain, backward and outwards into the tentorium cerebelli and terminates in the lateral sinus. It is proposed to refer to this vessel as the "basal vein." Until the basal vein reaches the lateral aspect of the mid-brain it corresponds in position fairly closely to the basilar vein in the human subject and it is joined by all the tributaries which are normally received in that part of its course by the basilar vein in man. Besides draining blood from the neighbouring structures the vein is joined by a number of important branches direct from the choroid plexus of the descending horn of the lateral ventricle.

The basilar vein in the dog begins in a plexus situated on the upper part of the lateral aspect of the mid-brain where it communicates freely with the tributaries of the basal vein. Its position is similar to that occupied in this part of its course by the basilar vein in man. Before terminating it turns sharply backwards and joins the great vein of Galen on its under surface. Not infrequently it unites with its fellow of the opposite side to form a common trunk. As the basilar vein courses round the crus cerebri it receives branches from the neighbouring cerebral convolutions, the mid-brain and the pulvinar. As already stated, it is in free communication with the thalamic branch of the vein of Galen.

As the great vein of Galen emerges from under cover of the splenium of the corpus callosum and ascends round its posterior border it is joined by a vein which runs from before backwards and rests on the superior surface of the corpus callosum. This is the inferior longitudinal vein. In the dog there is no sinus in the free lower border of the falx cerebri. The inferior longitudinal vein is the last tributary of note to be received by the great vein of Galen before it becomes the straight sinus at the anterior border of the tentorium cerebelli.

ANATOMICAL CHANGES FOLLOWING OCCLUSION OF THE GREAT VEIN OF GALEN.

From a consideration of the above account of the great vein of Galen and its tributaries it would appear probable that an obstruction applied to any part of its course may be compensated by the development of collateral circulation. It is proposed, therefore, to describe the conditions found on examining the brains of animals in which the great vein of Galen had been occluded at some point on its course for a period of not less than three months' duration.

As already stated, the occluding clip was found always to be enclosed in a fibrous capsule which involved the vein both in front and behind

the clip for a variable distance. In no instance, however, was there extensive obliteration of the vein beyond the clip, and frequently the vessel remained patent on either side directly up to the fibrous capsule.

There are three main sites at which the great vein of Galen may be occluded: the clip may be placed (1) on the anterior part of its course between its point of origin and the point where it is joined by the basilar veins; (2) at the point where it is joined by the basilar vein to obstruct all three vessels, or (3) on the posterior part of its course between the point where it is joined by the basilar veins and its termination in the straight sinus.

(1) In 18 cases a clip was placed successfully on the anterior part of the great vein of Galen, and in 13 of these it was discovered subsequently to be situated close to the origin of the vein. As already stated these cases are especially important, for Dandy and Blackfan claim that hydrocephalus occurs where the great vein of Galen is obstructed at its origin, if a sufficient time is allowed for its development. They are of the opinion that the hydrocephalus of venous obstruction is of slow and gradual onset. In three of the cases the veins of Galen were found to be obliterated at their termination by an extension of the scar tissue from the fibrous capsule surrounding the clip, but in all other instances they remained patent. From a consideration of fig. 2 it will be observed that the only tributaries of any consequence to be received by the great vein of Galen in the anterior part of its course are the veins from the choroid plexus of the third ventricle and the thalamic tributaries. As already stated, these vessels are subject to marked variations. In most instances they were torn and obliterated in the process of dissecting up the great vein of Galen from its bed previous to applying the clip; not uncommonly they were found to be involved by the clip itself or by the resulting scar, and even when not obliterated they did not appear to take any special part in the development of collateral circulation.

In all instances collateral circulation was found to have established itself through the medium of the thalamic tributary of the vein of Galen and the communications of this vessel with the basilar vein. The veins which drain blood from the plexus of the descending horn of the lateral ventricle into the basal vein were found to be dilated so that it would appear that a collateral circulation had also established itself in the substance of the choroid plexus. In no instance were the choroid

plexuses found to present any changes to naked-eye inspection. The cerebral ventricles showed variations in size which corresponded with those of normal controls.

(2) In four instances a clip was successfully placed to include the termination of both basilar veins together with the trunk of the great vein of Galen. On examination after death the occluded vessels were

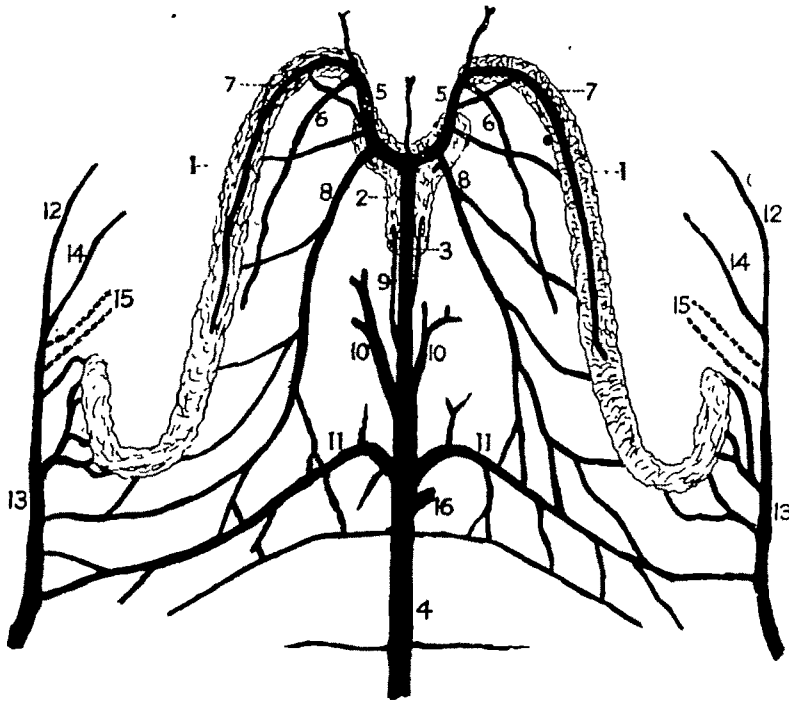


FIG. 2 —Diagrammatic representation of the veins of the velum interpositum and their main communications in the dog. The true relations of the various structures have been distorted and the vessels depicted as occupying one plane. 1. Choroid plexus of lateral ventricle. 2. Choroid plexus of third ventricle. 3. Great vein of Galen. 4. Straight sinus. 5. Vein of Galen. 6. Vein of corpus striatum. 7. Vein of choroid plexus of lateral ventricle. 8. Thalamic tributary of vein of Galen. 9. Tributary of great vein of Galen from choroid plexus of third ventricle. 10. Thalamic tributary of great vein of Galen. 11. Basilar vein. 12. Anterior cerebral vein. 13. Basal vein. 14. Sylvian vein. 15. Deep striate veins. 16. Termination of inferior longitudinal vein.

found to have remained patent close up to the fibrous capsule enclosing the clip. Anteriorly a collateral circulation had developed in the same way as after obstruction to the anterior part of the great vein of Galen. The blood from the basilar vein, now no longer able to enter the great vein of Galen, was found to have passed in a retrograde manner towards the base of the brain and to have escaped through communications

which have already been described into the basal vein. Here again, however, the marked dilatation of the veins which drain blood from the choroid plexus of the descending horn of the lateral ventricle into the basal vein provided definite evidence that a collateral circulation had also developed in the substance of the choroid plexus. The choroid plexuses remained normal to naked-eye inspection and the cerebral ventricles showed only those variations in size which are to be found in normal controls.

(3) The presence of the inferior longitudinal vein would seem to render it possible to occlude the posterior part of the great vein of Galen at two different sites: (a) The clip may be placed at the point where it is joined by the inferior longitudinal vein. In two cases the occluding clip was successfully placed on the posterior part of the great vein of Galen so as to include at the same time the termination of the inferior longitudinal vein. The junction of the basilar veins with the great vein of Galen remained patent. Collateral circulation was found to have established itself mainly through the communications of the basilar vein with the basal vein and it was evident that the blood from the obstructed great vein of Galen had escaped into the basilar vein and through these communications into the basal vein. The choroid plexuses presented no change to naked-eye inspection and the ventricles remained normal in size. (b) The clip may be placed posterior to the point of union of the inferior longitudinal vein with the great vein of Galen. From consideration of fig. 2, it will be observed that occlusion at this site is equivalent to occluding the straight sinus. In four cases a clip was placed on the posterior part of the great vein of Galen posterior to the point where it is joined by the inferior longitudinal vein. On subsequent examination the inferior longitudinal vein was found in all cases to be uninvolved by clot or scar. Contrary, however, to what might have been expected, the inferior longitudinal vein seemed to take no special part in the formation of collateral circulation which developed in the same way as after the simultaneous occlusion of this vessel and the great vein of Galen. The choroid plexuses remained normal in appearance and the cerebral ventricles presented no deviation in size from the normal.

In addition to the cases above recorded, the great vein of Galen was successfully occluded in nineteen other instances, but, either as a direct result of operation or of the onset of some acute infectious condition such as distemper, the animals died or had to be killed before they had survived a period of three months. In these cases the clip had been

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placed on the anterior part of the great vein of Galen in fifteen instances, and the survival period varied from less than a day to eight weeks. Except for the occurrence of toxic changes in the acute infectious cases, the findings were identical with those in animals which survived the full period. Collateral circulation seemed to have developed almost immediately after occlusion of the vein. In two cases the great vein of Galen was successfully occluded at the point where it is joined by the basilar veins, but one animal died after three weeks from lobar pneumonia and the other, owing to the onset of acute distemper, had to be killed after a period of seven weeks. Apart from changes due to the presence of an acute infection, the gross findings in the brain were identical with those in animals which had survived three months. Two animals in which the posterior part of the great vein of Galen had been successfully occluded had to be killed after three weeks owing to acute distemper. Here again, except for changes due to the presence of an acute infection, the findings were identical with those in animals which had survived three months.

From a consideration of the above findings, it would appear that as regards the development of collateral circulation the great vein of Galen can be occluded at only three different sites. The obstruction may be placed: (1) on the anterior part of its course, (2) at the point where it is joined by the basilar veins, (3) on the posterior part of its course.

THE CHOROID PLEXUSES AFTER OCCLUSION OF THE GREAT VEIN OF GALEN.

In all cases in which the great vein of Galen had been occluded, a careful examination was made to determine whether the choroid plexuses presented any change to naked-eye inspection. Special attention was paid to that part of the plexuses which occupies the body of the lateral ventricles. It appeared probable from a consideration of the venous return of the plexuses that this part would experience the most intense engorgement. In healthy animals killed in the standard way, the plexuses never presented any change to naked-eye inspection. Realizing, however, that histological changes may possibly take place without bringing about an alteration in gross naked-eye appearance, an attempt was made to examine the plexuses microscopically. This investigation, however, was far from successful. It was found impossible to obtain satisfactory histological preparations unless the brain was injected immediately after death with a formol saline solution. The plexuses from five cases were examined histologically. In three of these the

anterior part, and in two the posterior part, of the great vein of Galen had been occluded. A search was made for the presence of fibrosis, vascular obliteration, altered blood-pigment, and a tendency to simplification of structure owing to degeneration of villi. As far as could be determined from preparations which were often imperfect, the plexuses appeared to remain entirely unchanged. This investigation cannot, however, claim to be exhaustive, and it is conceivable that a more careful examination may reveal structural changes in the plexuses after occlusion of the great vein of Galen. It is realized, however, that even the absence of structural changes does not in any way exclude changes in the functional activities of the plexuses.

DISCUSSION.

From a consideration of the above experiments it would appear that hydrocephalus does not develop after occlusion of the great vein of Galen and that Dandy and Blackfan's finding of hydrocephalus in one case out of a series of ten was not due to obstruction of this vessel but was due to some entirely different cause. Since this work was first undertaken a valuable contribution to the subject has been made by Guleke [14]. This worker successfully occluded the great vein of Galen in nine dogs. In six of these the vein was divided near its origin. The cases survived from a few days to three months. On section eight were found to display no trace of hydrocephalus but one case presented it in a moderate degree. This animal was killed after a survival period of two and a half months. Guleke comments on the free manner in which collateral circulation develops after occlusion of the vein. Unfortunately, however, he does not indicate the precise way in which it is established. In another series of experiments which was primarily devised to investigate the formation of hydrocephalus after blocking of the aqueduct, Guleke occluded the great vein of Galen and the aqueduct either simultaneously or after an interval. Success was achieved in twelve cases and the animals survived from twelve hours to six weeks. Only two developed hydrocephalus; one died within twelve hours of operation and Guleke is of the opinion that the hydrocephalus was due more to operative trauma than to closure of the channels by which the cerebrospinal fluid is removed. In the second case the great vein of Galen had been occluded for two months and the aqueduct blocked for one month before death. As it is proposed in a later paper to consider the effects of experimental obstruction of the aqueduct in dogs, these latter experiments will not now be considered in detail.

It must, however, be admitted that as regards the effects of occlusion of the great vein of Galen, Guleke's findings are in harmony with those of Dandy and Blackfan. Unlike Dandy and Blackfan, however, Guleke does not conclude that simple occlusion of the great vein of Galen causes hydrocephalus; he is of the opinion that some additional circumstance must be present, but does not specify its nature. It remains, therefore, to provide some explanation for the occasional discovery of hydrocephalus in animals which have undergone the operation for occlusion of the great vein of Galen. On perusal of Dandy and Blackfan's and Guleke's papers one is impressed by the total absence of any account of a histological investigation of the hydrocephalic brain and its coverings. Hydrocephalus may occur spontaneously in dogs in association with a number of infective conditions, and it is conceivable that a hydrocephalus indistinguishable from that which Dandy and Blackfan claim to have been caused by obstruction of the great vein of Galen may be the result of an inflammatory lesion at the base of the brain. This lesion may be recent or of considerable standing, and without a careful histological investigation may be recognized only with the greatest difficulty. A search through the literature has failed to trace any account dealing with the precise character of the acquired hydrocephalus in dogs. Nevertheless, one cannot over-emphasize the importance of maintaining a guarded attitude towards the significance of the occasional discovery of hydrocephalus in dogs which have had the great vein of Galen occluded. Before any judgment can be reached it is essential that the brain and its coverings should first be submitted to a careful histological investigation. It is known from clinical observations on the human subject that a relatively high degree of hydrocephalus is compatible with fairly normal activities and behaviour, and it is conceivable that Dandy and Blackfan's and Guleke's animals had either acquired hydrocephalus prior to operation or subsequently to the onset of some form of meningo-encephalitis. Cushing [5] draws attention to the ease with which the arachnoid villi may be blocked by blood and the products of inflammation and expresses the opinion that Dandy and Blackfan have not paid sufficient attention to this aspect of the subject. On the other hand it may be that the total absence of hydrocephalus in the cases now under consideration was due mainly to the practice of killing all animals as soon as they developed an infective condition such as "distemper," a condition to which operated animals seemed to be especially liable. If these animals had not been killed a number would probably have survived the infection, and some of these might have developed a post-

infective hydrocephalus, of which the true nature could have been determined only by a careful histological examination. It is interesting to record that one unoperated animal developed hydrocephalus spontaneously, and although the hydrocephalus was subsequently found to be due in all probability to an obstruction of the aqueduct by organizing inflammatory exudate, the case illustrates the difficulty of determining the nature of a hydrocephalus by mere naked-eye inspection.

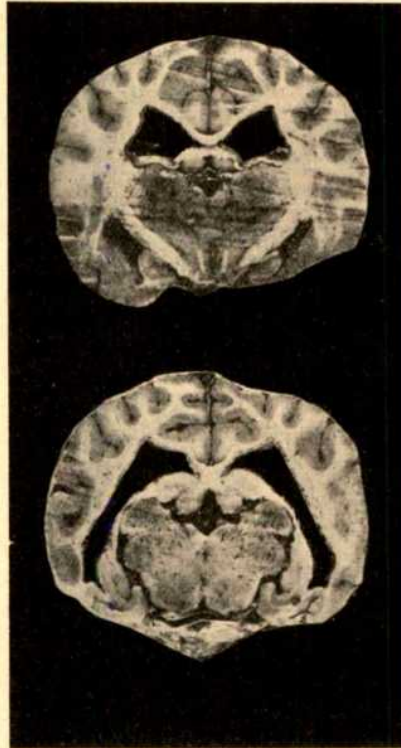


FIG. 3.—Transverse sections through the brain of a dog which developed hydrocephalus as a consequence of meningo-encephalitis. The aqueduct was found to be partly blocked by organizing exudate.

An unoperated dog, aged about 12 months, which had been in the laboratory for about three weeks, suddenly had a convulsion and vomited its food. On examination it was found to be somewhat dull and to have a paresis of the hind limbs. No more convulsions were observed, and a few days later, except for the paresis of the hind limbs, the animal appeared to be normal. A week later the paresis began to improve, but although the dog was ultimately able to stand on all four legs the power

of walking never returned completely. After six weeks the animal unexpectedly developed pneumonia and died. At autopsy the brain and meninges appeared to be markedly injected, but they presented no clear evidence of meningitis. No exudate was visible on naked-eye inspection. The cord and its coverings appeared healthy. On sectioning the hardened brain, both lateral chambers were found to be dilated. The aqueduct, however, was not dilated (fig. 3). Histological examination revealed a generalized meningo-encephalitis. The lesion appeared to be subsiding, and the aqueduct was found to have lost its ependymal lining and to be partly blocked by organizing exudate. The spinal cord presented no change. During life repeated ophthalmoscopic examinations failed to reveal the presence of papilloedema.

(3) *The Causation of the Increased Intracranial Pressure associated with the Cerebral Tumours.*

No account of the effects which follow compression of the great vein of Galen would be complete without a reference to Stopford's theory of the origin of the increased intracranial pressure, which is frequently associated with cerebral tumours. While it is not proposed to consider this attractive theory in detail, reference will be made to its most important aspects. In 1926 Stopford [23] expressed the opinion that in man "the great vein of Galen is situated in such a position that it may be compressed against the splenium of the corpus callosum indirectly by tumours occupying sites which are known to give rise most constantly to increased intracranial pressure," and that "such compression is not so likely in the case of tumours occupying situations which are known to cause less frequently increased intracranial pressure." He accepted Dandy and Blackfan's experimental work on the great vein of Galen and suggested "that moderate compression without complete occlusion of the vein is likely to give rise to increased intracranial pressure accompanied by slight or negligible dilatation of the ventricles." In a subsequent paper [24] he concluded, "it seems likely that raised intracranial pressure associated with tumours within the cranium is more commonly due to compression of the great vein of Galen than to any other cause." It would be idle to deny the attractive nature of this explanation of the origin of the increased intracranial pressure of cerebral tumours which certainly accounts for many of the associated phenomena. In order, however, to establish it on a firm basis, it is desirable to prove at the outset (1) that the great vein of Galen is actually obstructed in cases of cerebral tumour associated with hydrocephalus and not in those

in which hydrocephalus is absent, and (2) that compression of the great vein of Galen gives rise to a formation of cerebrospinal fluid which is so excessive that the absorption mechanism is unable to deal with it.

On anatomical grounds and from actual observations, both clinical and pathological, on cases of cerebral tumour Stopford has demonstrated that it is highly probable that the great vein of Galen may be indirectly compressed by subtentorial tumours or by tumours situated in the posterior part of the cerebral hemispheres. Unfortunately, however, the evidence remains largely indirect and no direct demonstration of actual obstruction of the great vein of Galen in the manner Stopford's theory demands has yet been made on the brains of subjects who have died from cerebral tumour. If such evidence were available the theory would be considerably strengthened. It might be thought that the histological appearance of choroid plexuses removed from cases of cerebral tumour would provide evidence that the great vein of Galen is compressed. Saito [22] and Ikedo [16] found the plexuses from the cerebral tumour cases to be oedematous and congested and detected swelling of the endothelial cells. Davis [9] was unable to discover any characteristic lesion, while Zand [26] described changes which were mainly degenerative and corresponded with those found in senile plexuses. Unfortunately these changes may have been induced by a number of causes other than obstruction of the great vein of Galen. Careful controlled work in this direction seems urgently to be needed.

Stopford presents no direct evidence that an increased formation of cerebrospinal fluid follows compression of the great vein of Galen, but seems to rely largely on Dandy and Blackfan's observations on dogs. Although in the experiments described here hydrocephalus did not follow occlusion of the great vein of Galen no matter at what point on its course the obstruction was placed, it would be false to conclude that compression of this vessel in man does not give rise to increased intracranial pressure. Such a view may be criticized on the following grounds: (1) The anatomical arrangement and connections of the veins of the velum interpositum of the dog differ from those found in man; (2) although in the dog total obstruction of the great vein of Galen does not, owing to the plexus-like nature of the veins of the velum interpositum, result in complete stasis, it is possible that if this vessel is actually compressed in man, the obstruction may be both incomplete and intermittent in character. Unfortunately it seems impossible to devise a method by which intermittent compression over long periods could be applied successfully to the great vein of Galen of the dog; (3) while in

the dog it is possible to exclude the presence of hydrocephalus it is difficult entirely to exclude the existence of a state of increased intracranial pressure. It is conceivable, although highly improbable both on clinical and post-mortem evidence that some of the operated animals, although failing to present at autopsy any evidence of dilatation of the ventricles, may have experienced during life increased intracranial pressure.

To sum up, it would seem justifiable to conclude that until conclusive evidence becomes available that an increased formation of cerebrospinal fluid follows compression of the great vein of Galen, any explanation which seeks on such a basis to account for the increased intracranial pressure associated with cerebral tumours cannot be regarded as having advanced beyond the stage of speculation.

SUMMARY.

(1) The authenticity of the two cases of hydrocephalus which Dandy considers to have been caused by obstruction of the great vein of Galen or of the straight sinus is open to question, and evidence is advanced that no indisputable case of hydrocephalus following thrombosis of these venous channels has so far been recorded.

(2) The arrangement and communications of the veins of the velum interpositum of the dog are described and are not identical with those found in man.

(3) After occlusion of the great vein of Galen, no matter at what point on its course, collateral circulation is rapidly established. The choroid plexuses remain unchanged in their gross appearance.

(4) In the dog hydrocephalus does not follow experimental occlusion of the great vein of Galen. It is suggested that the hydrocephalus which was found occasionally by Dandy and Blackfan and by Guleke in dogs in which the great vein of Galen had been occluded was not due to obstruction of this vessel but was of an entirely different aetiology. The hydrocephalus is most easily explained as having its origin in some form of meningo-encephalitis which has led to an obstruction of the normal circulation of cerebrospinal fluid at the base of the brain.

My thanks are due to Dr. A. D. Macdonald for assistance during the operations, to Dr. L. B. Winter for a supply of control material, to Dr. E. T. Ruston for help with histology and to Dr. Cave of the Anatomy Department of the Leeds Medical School for his kindness in checking my observations on the anatomy of the veins of the choroid plexus of the dog. To Professor Tom Hare of the Royal Veterinary College my

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PROGRESSIVE PARALYSIS OF THE NERVUS INTEROSSEUS DORSALIS.

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FROM time to time we have been confronted with cases of isolated paralysis affecting the nervus interosseus dorsalis, in none of which has a satisfactory explanation of the paralysis been forthcoming. In one case, in which the affected nerve was explored, the only apparent explanation was an anatomical peculiarity of the course of the nerve. A search of the literature has brought little enlightenment, and we are prompted to report our cases in the hope that subsequent investigation may shed light on this singular affection.

REVIEW OF LITERATURE.

Reports of cases of isolated paralysis of the nervus interosseus dorsalis are not common, and in the majority of cases there had been a traumatic origin; for example, after a gunshot wound [6, 8], after a wound by a circular saw [7], and after a sprain intensified by pressure on the nerve during sleep [1].

In the case recorded by Jumentié [4], the paralysis was gradually progressive; the weakness involved the musculus extensor digiti quinti proprius and the adjacent part of the musculus extensor digitorum communis; finally the fourth and fifth fingers could not be extended at their metacarpophalangeal joints, and the affected muscles showed the reaction of degeneration. On the dorsum of the wrist and extending up the fore-arm was a swelling thought to be due to synovitis. We have seen a somewhat similar case in which the nerve was involved in a tumour near the elbow, but we do not propose to include this case in the present paper.

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The details of a case reported by Guillain and Courtellement [2] most nearly resemble those of our own cases.

In July, 1903, a man, aged 40, whose previous history included the possibility of syphilitic infection, found that he was unable easily to extend the fifth finger of his right hand. Ten days later the same disability appeared in the fourth finger. The paralysis spread, and by December, 1903, extension of the third finger became impaired. Subjective and objective sensory disturbances were both absent throughout. At the time of examination the palsy had existed for ten months. Tenderness could be elicited on the posterior surface of the fore-arm, over the point of entrance of the nervus interosseus dorsalis into the fibres of the musculus supinator radii brevis. The paralysis was limited to the extensor muscles of the third, fourth and fifth fingers, and in these muscles partial reaction of degeneration could be demonstrated. The patient was conductor of an orchestra and had held his baton usually with the fourth and fifth fingers; the writers attributed the paralysis to the repeated movements of pronation and supination necessary in his professional work, and they advised the patient to interrupt this.

A sensory counterpart of the motor affection under review was described by Wartenberg, [9] under the designation "*cheiralgia paraesthetica*"; he regarded the condition as being due to neuritis of the ramus superficialis nervi radialis, and as being analogous to *meralgia paraesthetica*. The clinical features of his five cases included lively *paraesthesiae* or pains along the radial side of the hand, thumb and index finger as well as impairment of sensation in this area, and pain on traction upon or percussion of the affected nerve. In one of his cases, the symptoms appeared seven weeks after a punctured wound which had presumably injured this nerve; in another, pressure of the band of a wrist watch was evidently responsible; in a third, exposure to cold might have been a factor, and in three cases the condition was attributed to over-exertion, but he assumed that a constitutional predisposition might play an important part. In all his cases improvement took place, but residual discomfort persisted in several cases for as long as two and a half years.

PERSONAL CASES.

Case 1.—In September, 1921, a woman aged 43, by occupation a store clerk, presented herself at the Mayo Clinic complaining of weakness of the left hand. Eight years previously, while wrapping bundles of coffee, she had noticed that the left fifth finger "*quivered*" occasionally. Gradually progressive weakness of the extensor movements of the fingers and wrist had made its appearance. Six and one-half years previously, she had undergone an operation elsewhere for removal of a left cervical rib, but this procedure was not followed by improvement.

On examination it was found that there was complete inability to extend the third, fourth and fifth fingers of the left hand; musculus extensor carpi ulnaris was also functionless. There was some atrophy of the muscles on the dorsal surface of the left fore-arm, which measured 2 cm. less in circumference than its fellow. Roentgenograms disclosed bilateral cervical ribs. Otherwise the examination was entirely negative.

A recent attempt to trace the subsequent history of this patient had been unsuccessful.

Case 2.—In April, 1921, a farmer's wife, aged 37, came to the clinic complaining of weakness of the right hand. At the age of 13 she had been allowed to discontinue instruction on the piano because of difficulty in extending the fifth finger of the right hand. During the three years preceding her examination, this disability had spread to involve other fingers.

The patient was a moderately obese woman. All the muscles of the right fore-arm innervated by the nervus interosseus dorsalis were completely paralysed and markedly atrophied. Exploratory operation with a view to tendon-transplantation was refused.

Case 3.—In March, 1920, a student, aged 17, sought advice at the clinic because of weakness of the right hand. Four years previously he had survived a severe illness due to rupture of the appendix. Two and a half months after this illness he had discovered that he could not extend the fifth finger of the right hand, and a week later extension of the remaining fingers became impaired; somewhat later still, extension of the thumb became reduced. The paralysis had increased gradually.

On examination it was found that power of active extension of the fingers and thumb was lost. The extensors of the wrist were intact. Reaction of degeneration was present in the paralysed muscles, and the circumference of the right fore-arm was 1 cm. less than that of the left fore-arm. A tender point was discovered over the course of the nerve, 7 cm. below the elbow-joint. Exploration of the nervus interosseus dorsalis was advised, but the patient did not return for this. In 1933 the condition was reported to be unchanged.

Case 4.—In August, 1927, a woman, aged 39, came to the clinic because of a goitre, which had been present since the age of 12. This proved to be a hyperfunctioning adenoma, and thyroidectomy was performed. Four months before her admission she had had pain in the left wrist, left ankle and both knees. One month later she had had a sore throat, accompanied by fever; one month after this she had observed that she could not extend the left thumb.

On examination it was found that there was complete paralysis of the M. abductor pollicis longus and the M. extensores pollicis. Infected tonsils and teeth were removed and light treatment and massage advised. On March 20, 1933, the patient wrote: "The condition is exactly the same. I am still

unable to move my thumb upward, to which I have grown accustomed. I am no longer troubled with the rheumatic pains."

Case 5.—A married woman, aged 34, came to the clinic April 13, 1932, on account of inability to extend the fingers and wrist of the right hand. Three years before she had noticed that she could not extend the fifth finger; six months later the weakness extended to the fourth finger and subsequently the third and second fingers and thumb were affected in that order. One year previously she had noticed wasting on the dorsum of the right fore-arm, and occasionally there had been twinges of sharp shooting pain in that region. The removal of infected teeth two years previously had not retarded the progress of the paralysis. When asleep she habitually kept the right fore-arm under the head.

On examination almost complete paralysis was found of all the muscles supplied by the nervus interosseus dorsalis distal to its branches to musculus extensor carpi radialis brevis. Sensation was intact. Exploration of the nerve was advised and was performed April 19, 1932. A longitudinal incision was made over the interval between musculus extensor carpi ulnaris and musculus extensor digitorum communis. When the supinator brevis was exposed it was found that instead of passing through the supinator the nerve passed superficially between this muscle and the aponeurosis of the common extensor. The nerve had moulded a groove across the fibres of the supinator, and it seemed possible that repeated mechanical trauma imposed on the nerve by the contractions of the supinator brevis might have given rise to neuritis. A direct faradic response to stimulation of the nerve was obtained from the muscles both of the superficial and deep groups, although it was slight in musculus extensor carpi ulnaris and musculus extensor communis digitorum.

In an endeavour to reduce the pressure on the nerve a strip of the extensor aponeurosis, 0.5 cm. in width, was excised over the course of the nerve, and the muscles of the superficial layer were not sutured.

On February 27, 1933, the patient wrote that there had not been any return of power.

ANATOMICAL CONSIDERATIONS.

The normal course of the nervus interosseus dorsalis is through the substance of the supinator brevis muscle. At the lower border of this muscle two branches of distribution appear; one innervates musculus extensor digitorum communis, musculus extensor digiti quinti proprius and musculus extensor carpi ulnaris; the other supplies musculus abductor pollicis longus, musculus extensor pollicis brevis, musculus extensor pollicis longus and musculus extensor indicis proprius (fig. 1). Two anomalous courses are described in anatomical textbooks. In that described by Harburger [3] the branch for the deep group of muscles is divided into two; one twig appears in

the usual situation and proceeds to supply musculus extensor pollicis longus and musculus extensor indicis proprius, the other passes through

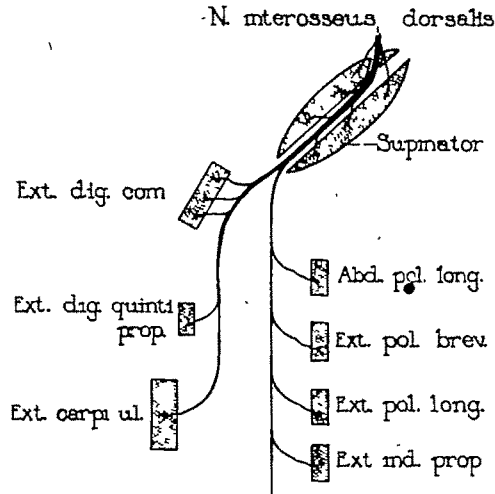


FIG. 1.—Schematic representation of the normal course and distribution of nervus interosseus dorsalis.

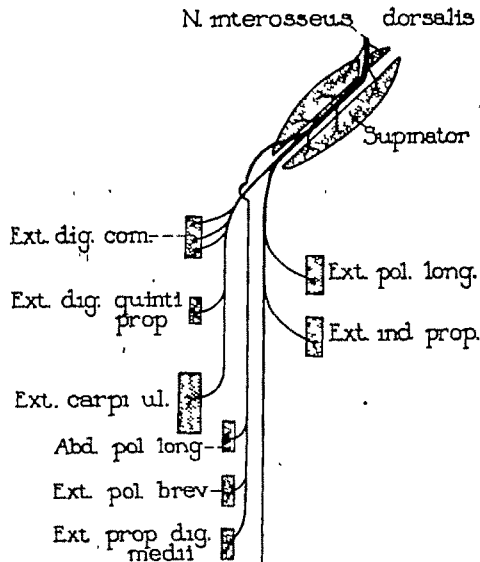


FIG. 2.—Anomalous course and distribution of nervus interosseus dorsalis described by Harbarger.

the substance of musculus supinator brevis to appear some distance above its lower border, and is distributed to musculus abductor pollicis longus, musculus extensor pollicis brevis and to a special musculus

extensor proprius digiti medii (fig. 2). The anomaly described by Luschka and by Krause [5] approximates to the arrangement found at operation in our Case 5; the branch of nervus interosseus dorsalis destined for the muscles of the deep group pursues a course superficial to the supinator brevis (fig. 3). This course was taken by the whole nerve in our own case.

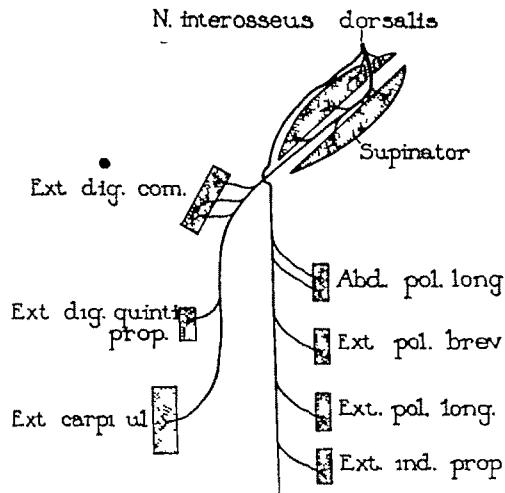


FIG. 3.—Anomalous course and distribution of nervus interosseus dorsalis described by Luschka and by Krause.

COMMENT.

The histories and findings of the patients in our own series of cases have been stripped of all irrelevant details; careful general physical and neurological examinations were made in all, and laboratory data including serological tests and roentgenograms were negative except where reported. In all the cases the paralysis was progressive; as a rule it began with weakness of the extensors of the fifth finger and extended radialward to involve both superficial and deep branches of the nerve. In no instance did the paralysis exceed the distribution of the nervus interosseus dorsalis, and in none were there objective sensory changes although pain was occasionally felt in the fore-arm. Unless some anatomical basis exists, such as seemed likely in the patient whose nerve was explored, we are at a loss to explain the disability. The absence of post-operative improvement in this case is not conclusive evidence against such an anatomical basis; for it is possible that by the time operation was undertaken the interstitial changes in the nerve were already irremediable.

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SUBDURAL FALSE MEMBRANE OR HÆMATOMA
(PACHYMENINGITIS INTERNA HÆMORRHAGICA)
IN CARCINOMATOSIS AND SARCOMATOSIS OF THE
DURA MATER.

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WE report in this paper four cases of subdural false membrane or hæmatoma, occurring with metastatic malignant disease of the dura. The association of these pathological conditions with one another is of no great clinical importance, but is of considerable pathological interest since it shows one manner in which subdural hæmatoma can be produced. When we speak of subdural hæmatoma we signify the condition described by different workers under such various terms as "pachymeningitis hæmorrhagica interna," "subdural false membranes," "meningeal apoplexy," "traumatic subdural hæmatoma," and so forth. The pathological lesion is a layer of very vascular granulation tissue which encloses a variable amount of organizing blood-clot and chocolate-coloured fluid and lies between the dura and the arachnoid, usually on the convex surface of one or both cerebral hemispheres. The names employed to describe the condition indicate the diversity of ideas about its nature.

Our attention was first drawn to the combination of subdural hæmatoma and malignant disease of the dura by Case 1 in which an unsuspected subdural hæmatoma was found at operation in a case of malignant disease of the roof of the orbit and overlying dura. Shortly afterwards a second example (Case 2) was encountered in the post-mortem room and subsequent investigation of the records and material of the Bernhard Baron Institute of Pathology at the London Hospital disclosed five further cases.

REPORT OF CASES.

Case 1.—*Secondary carcinoma of the roof of the right orbit and dura. Subdural hæmatoma. Operation: Partial removal of the tumour and hæmatoma.*

History of illness.—J. J., a man aged 64, was first seen on April 21, 1933. Early in 1932 the sight of his right eye became blurred and for ten weeks the

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eyelids were closed. When they opened again there was diplopia and from that time the eyeball became increasingly prominent. There was slight pain in the right eye, later becoming severe. Early in 1933 pain spread to the right zygomatic region and at times to the upper and lower jaw. For a few weeks before admission to hospital his memory was slightly impaired. During the illness he lost 6 kg. in weight and suffered from sciatica in the right leg.

Examination.—Speech and mentality appeared to be normal. There was slight swelling in the right temporal region above the zygoma and the right superficial temporal artery was more prominent than the left. Smell was completely lost at both nostrils. The right optic disc was pale and its edges were blurred; there was no measurable swelling but the retinal veins were engorged. Visual acuity: right, $\frac{2}{36}$; left, $\frac{6}{12}$. Vision in the right eye was limited to the isopters within 25° and mainly above the horizontal meridian. The field and fundus of the left eye were normal.

The right pupil reacted sluggishly to light. There was great displacement of the right eyeball forwards and also slightly downwards, and great diminution of all its movements, especially in an upward direction. The right upper eyelid drooped and there was chemosis of the ocular conjunctiva. Immediately below the inner part of the right supra-orbital ridge a firm, tender nodule, about 2 by 1 cm., could be felt beneath the skin. The right cornea was insensitive. No other neurological signs were found.

There was considerable bronchitis and emphysema, severe osteo-arthritis of the interphalangeal joints of the fingers and of the right hip and both knee-joints. The prostate was enlarged and firm and on the left side slightly nodular. By percussion there was evidently a moderate amount of residual urine. Blood-pressure 145/90 mm. Hg. X-rays showed a large hyperostosis of the roof of the right orbit extending from the supra-orbital ridge to the right anterior clinoid process. This bony thickening appeared to involve also the right frontal and ethmoidal sinuses. The diagnosis made was meningioma of the right side of the olfactory groove invading the frontal and ethmoid sinuses.

Operation, April 29, 1933. The right frontal region was exposed through an osteoplastic flap. Fragments of soft white tumour tissue were found between the pericranium and temporal muscle. The dura over the roof of the orbit and in the adjacent temporal region was thickened by tumour and a thin film of tumour extended upwards over the outer surface of the dura along the course of the meningeal vessels. The inner surface of the dura over the roof of the orbit presented numerous plaques and small nodules of white tumour tissue, but there was no large intradural mass of tumour. The bony roof of the orbit was everywhere thickened, in places up to 1 cm. thick. In the orbit immediately beneath this thick bone was a layer of white tumour.

The dura over the convex surface of the right frontal lobe appeared externally to be normal. When it was opened a glistening dark red

membrane about 0.3 cm. thick was found covering the frontal lobe (fig. 1). It was easily detached from both dura and arachnoid and it extended back beyond the posterior limits of the incision. No fluid was found within this membrane. The roof of the orbit was partially removed, but not so far as to expose the ethmoidal or frontal sinuses, for it was obvious that the tumour was malignant and irremovable. A subtemporal decompression was also made, and fragments of dura and subdural membrane were removed for histological study.

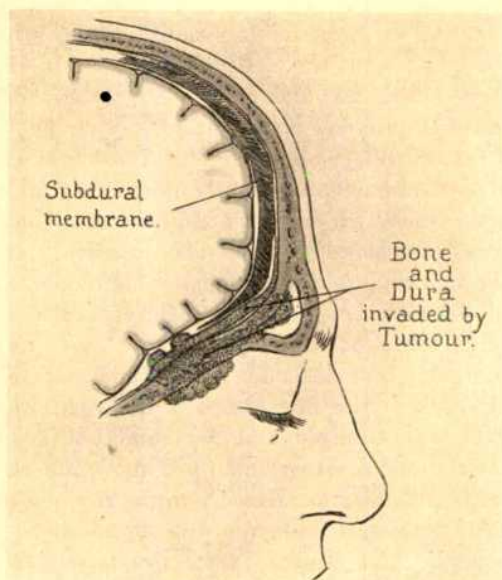


FIG. 1. Case 1.—Diagram showing the findings at operation.

Subsequent course.—Recovery from operation was uneventful except for temporary difficulty with micturition. There was complete relief from headache and some recession of proptosis, but no recovery of vision in the right eye. X-ray therapy was applied to the right orbit and right fronto-parietal region. Six months later the condition of the right eyeball was practically unchanged and there were no further cranial symptoms, but the patient was suffering from pain in the right sacral region, so severe as to suggest that the sacrum might be invaded by tumour.

Pathological Examination. (S.D. 865/33).

Macroscopic examination.—The material consisted chiefly of portions of skull and adjacent dura that were visibly infiltrated with growth and had been fixed in 4 per cent. saline formaldehyde. The largest piece of dura was a crescentic slip 5 cm. long and up to 2.5 cm. broad. The

outer surface was rough, gritty, and stained chocolate brown from hæmorrhage. In places a little greyish-white growth was present. Lightly attached to the inner surface were some smooth discrete bosses of pearly-grey growth varying in diameter from 0·3 cm. up to 1·3 by 1·7 cm. The remainder of the inner surface was coated with a translucent buff coloured membrane varying in thickness from less than 0·05 cm. to 0·1 cm. This could easily be stripped from the dura, leaving a smooth orange-coloured surface.

There were also two small rectangles (1·3 by 0·9 cm.) of dura which were macroscopically free from growth. These had been removed from the posterior part of the area exposed at operation and fixed in formaldehyde and Zenker's fluid respectively. The inner surface of each of these was covered with a semi-translucent café-au-lait membrane (0·15 cm. thick) which tended to separate from the dura.

Microscopic examination.—Paraffin blocks were prepared from transverse sections of the dura with buff-coloured membrane and nodules of growth, from portions of the calvaria, after decalcification with nitric acid, and from the rectangles of dura with café au lait membrane and no obvious growth. Sections in this and in subsequent cases were stained with hæmatoxylin and eosin, Weigert's iron hæmatoxylin and van Gieson's mixture, Weigert's fuchselin and neutral red, and, after treatment of formalin-fixed tissue with Zenker's fluid, with phosphotungstic acid-hæmatoxylin.

The tumour is a solid acinar and tubular, polygonal celled carcinoma. There are no special features about the cells that enable the primary site to be identified. In the dura with macroscopic nodules of growth there is extensive carcinomatous infiltration of the outer (periosteal) of the two dense fibrous layers of the dura, associated with a chronic inflammatory infiltration and much recent hæmorrhage. A few trabeculæ of bone are present in the outermost part of this zone. There is little growth in the inner dense layer and it is confined to the lumina of veins and capillaries. Around these vessels is a little infiltration with small lymphocytes and fibroblasts. The areolar layer is thickened and forms the membrane seen with the naked eye. In most places it is occupied by large solid bosses of carcinoma cells; elsewhere it resembles granulation tissue, being composed of very numerous fibroblasts and young capillaries. Many of these capillaries are plugged with growth. In places there are patches of recent hæmorrhage.

In the rectangular pieces of dura without macroscopic growth the membrane that forms the under-surface proves also to be the areolar layer of the dura, greatly thickened. It is as thick as or thicker than

the two dense layers of the dura together (fig. 2). It is composed of a granulation tissue in which numerous spindle fibroblasts containing fibroglia fibrils are interspersed with delicate collagenous fibrils, macrophages containing brown pigment, and small lymphocytes. Within it there is much fibrin, and also recent diffuse hæmorrhage. In places upon its surface are collections of red corpuscles. Many capillaries and veins are enormously dilated and engorged. Some of them are plugged with tumour cells (fig. 3), but others are distended with blood. There are very few tumour cells outside the vessels. The dense layers are unaltered except that capillaries and veins here also are distended with tumour cells; the arteries are free of tumour. Some arteries show reduplication of the elastic lamina. The fragments of calvaria show infiltration of the medullary spaces with masses of tumour cells.

Comment.—This is a case of secondary carcinomatosis of the roof of the orbit and overlying dura associated with subdural hæmatoma. There is a certain amount of clinical evidence that the primary tumour may have been situated in the accessory nasal sinuses or in the prostate. The clinical resemblance of the case to meningioma en plaque of the orbital dura is also of considerable interest. These features, however, are not relevant to our present thesis, which concerns the subdural membrane found at operation. This membrane had given no symptoms before operation, doubtless because of its tenuity. Histologically, however, it is identical with that found in large traumatic or idiopathic subdural hæmatomas. It occupies the areolar layer of the dura which is transformed into a layer of granulation tissue containing numerous greatly dilated and engorged capillaries and veins, areas of recent hæmorrhage, and macrophages containing brown pigment. It is not a reaction to the presence of tumour cells, for these are not present in some parts of the membrane, and when present they are almost entirely confined to the lumina of its vessels. Extension of the tumour in the dura over the frontal lobe has taken place not by direct spread but by permeation of veins and capillaries (fig. 3). The cases that follow suggest that it is the venous obstruction caused by this manner of spread that is of significance in the production of subdural hæmatoma.

Case 2.—*Subdural hæmatoma. Secondary carcinomatosis of calvaria and dura mater. General carcinomatosis. Primary diffuse scirrhus carcinoma of stomach. Operation: laparotomy.*

E. B., a woman, aged 65, had complained for one year of abdominal pain, vomiting and loss of weight.

On examination a tender mass was felt in the epigastrium, and at operation an inoperable carcinoma of the stomach and numerous intraperitoneal metastases were found. She died ten days after operation, being delirious and finally unconscious in the two days before death.

Summary of Necropsy. (P.M. 269, 1933.)

Moderately contracted stomach with diffuse scirrhus carcinomatous infiltration of its middle part. No ulceration. Secondary carcinomatous deposits in gastro-coronary, coeliac, peripancreatic, lumbar and mesenteric glands. Extensive secondary carcinomatosis of peritoneum of mesentery. Secondary carcinoma of both suprarenal bodies. Secondary carcinomatosis of marrow of right femur, right humerus, ribs and lumbar and lower six thoracic vertebræ. Four small plaques of secondary growth (up to 1 by 0.6 by 0.15 cm.) in submucosa of jejunum. Faint miliary nodules and streaks of growth in very injected periosteum over vault of skull.

Hæmolytic staining of endocardium and intima of all vessels and less conspicuous of other tissues. Parenchymatous degeneration of myocardium. Considerable general atheroma. Post-mortem degeneration and moderate bacterial emphysema of liver. Moderate emphysema and slight myeloid reaction in pulp of spleen. Parenchymatous degeneration of kidneys. Acid digestion of posterior parts of lungs. Atrophy of uterus and of ovaries. Recession of gums from carious teeth. Hirsuties of face. Superficial pressure erosion on each buttock. A slightly wasted, fat woman.

Brain and Meninges.—On removing the top of the skull the outer surface of the dura was roughened, especially over the middle meningeal arteries, by numerous fine linear and pinhead yellowish-white tags, and showed a diffuse brownish discoloration in the frontal region and alongside the superior longitudinal sinus. Grey and pinkish-grey, granular, somewhat dry, lightly adherent ante-mortem thrombus occupied the anterior 6 cm. of this sinus. The sinuses elsewhere contained fluid blood except that a few opaque yellowish-white nodules (up to 0.7 by 0.3 by 0.2 cm.) were attached to the intima of the lateral sinuses, especially the right. During removal of the calvaria the subdural space was accidentally opened and about 60 c.c. of fluid blood with a faint brownish tinge escaped from the right side.

The inner surface of the dura covering the cerebral convexities was everywhere coated with a translucent café-au-lait membrane, varying in thickness from less than 0.05 up to 0.15 cm. This extended on to the falx but was not present in the posterior fossa, nor on either surface of the tentorium cerebelli. There was extensive hæmorrhagic mottling of the membrane, and in many places thin sheets of recent blood-clot appeared to lie within it. Over the right parietal region a mass of

clot (6 by 3 by up to 0.5 cm. thick) was in places attached to the dura and formed a direct continuation of the membrane. Elsewhere it was unattached, and exposed an apparently intact membrane coating the inner surface of the dura. In many places the dura, on section, appeared to be thickened by ill-defined plaques (up to about 3 cm. diameter and from less than 0.05 to 0.1 cm. deep) of firm creamy grey tissue resembling growth.

On the surface of the cerebral convexities were a few shallow depressions. On the right a long comma-shaped depression stretched from 4 cm. behind the frontal pole to the parietal lobe. The expanded hinder end of this depression corresponded with the mass of clot already described. On the left were two small saucer-like depressions over the frontal and parietal lobes respectively. The leptomeninges in these areas had a cloudy, gelatinous appearance, and the sulci were distended with clear faintly straw-coloured fluid. No membrane could be detected on the surface of the arachnoid. On frontal section, after hardening in formaldehyde, the brain appeared normal except for a few cavities in the cerebral white matter caused by post-mortem gas-bacillus infection.

Microscopic examination.—Five strips of dura were selected for paraffin sections from different parts, including the margin of the clot over the right parietal lobe, the margin of a plaque of growth, a transverse section of the left middle meningeal artery, the anterior part of the superior longitudinal sinus and an intimal nodule in the right lateral sinus. In addition a strip of dura was cut on the freezing microtome, and sections were stained with scharlach R and hæmatoxylin. A piece of the bony vault from the frontal region was decalcified in nitric acid and embedded in paraffin. Lastly paraffin sections were prepared from two blocks of the cerebral cortex with its leptomeninges from the right frontal lobe and left Sylvian fissure respectively.

Skull and periosteum.—Many of the medullary spaces, especially in the inner third, contain groups of round and polygonal carcinoma cells. These are associated with many spindle fibroblasts. Islands of coarse-fibred bone are found in several places in the centre of the medullary spaces and on the margins of trabeculae bounding spaces. The periosteum is greatly infiltrated and thickened by secondary carcinoma and an associated fibroblastic reaction. The capillaries here are greatly engorged. Some have ruptured with extravasation of red corpuscles; others are distended with plugs of tumour cells. There is a little inflammatory infiltration with neutrophil leucocytes and small lymphocytes.

Dura mater.—The changes in the dura vary in different places

according to whether or not the lumina of veins and capillaries are permeated with growth. In a few places, and these are often adjacent to areas with extensive permeation, the whole thickness of the dura is free from growth. The veins and capillaries here are greatly engorged and in places contain a little fibrin. The areolar layer in such areas is slightly thicker than normal from the distension of capillaries and a slight excess of spindle fibroblasts about them. A little diffuse hæmorrhage is sometimes present within it. From such areas there is a sudden transition to others where a considerable or even great thickening of the areolar layer by granulation tissue is associated with a conspicuous permeation of veins and capillaries with tumour cells (fig. 4). Such permeation affects vessels in all layers of the dura but is most conspicuous in the inner dense and areolar layers. The lumina contain a considerable amount of fibrin as well as tumour cells, and organizing thrombus is present in some. Vessels that are not permeated are greatly engorged and hæmorrhages are frequent in their neighbourhood. The extravasated blood sometimes forms a film on the inner surface of the areolar layer and in places such films are undergoing organization. The tissue in the areolar layer is rich in fibrin, spindle fibroblasts and macrophages containing ingested red corpuscles, fatty substances and pigment. A few small lymphocytes are present here and there. In places, especially near the inner surface, a few delicate collagenous fibrils are present.

The dense layers of the dura show, in Herxheimer preparations, a diffuse fatty degeneration, the fatty particles being arranged in longitudinal streaks along the collagen fibres.

The lumen of the superior longitudinal sinus is occupied by ante-mortem thrombus in which groups of tumour cells are present. A nodule attached to the intima in the right lateral sinus is of similar structure.

The arachnoid membrane over the cerebral cortex has undergone collagenous thickening. The meshes of the underlying pia-arachnoid contain here and there small groups of polygonal cells with round or irregularly lobed nuclei and a vacuolated cytoplasm. They are probably desquamated lining-cells of the pia-arachnoid. In the cortex of the right frontal lobe one perivascular space is infiltrated with cells resembling tumour cells.

Comment.—In this case as in Case 1 a subdural membrane was found in association with extensive carcinomatosis of the dura. On the left side the dura was covered with a membrane of dimensions similar to

that which was found in Case 1. On the right side there was a similar membrane and in addition a mass of clot and a collection of about 60 c.c. of brownish fluid blood which escaped when the dura was opened. With the exception of the terminal delirium and coma there were no symptoms during life that could be attributed to the intracranial condition.

In this case the primary carcinoma of the stomach had given rise to numerous metastases in bones, including the skull. Spread to the dura was by way of the blood-stream: numerous veins and capillaries in all layers of the dura were plugged with tumour cells, and collections of tumour were also found in the superior longitudinal and right lateral sinus. Veins and capillaries not filled with tumour were greatly engorged. It is this engorgement of vessels of the areolar layer of the dura which appears to be the primary factor in the formation of the subdural membrane. The case which follows shows a much earlier stage of the process.

Case 3.—Subdural membrane. Secondary carcinomatosis of dura, skull, long bones, etc. Primary carcinoma of lung.

A. F., a man, aged 44, became ill with pain in the muscles, especially those of the left buttock, seven weeks before his death. He could not sleep, and was depressed, and a few days before his death he became delirious. As a young man he had had syphilis but the Wassermann reaction was negative in the blood taken at necropsy and in the cerebrospinal fluid. The cerebrospinal fluid on the day before his death contained three small lymphocytes per c.mm. and 0.03 per cent. of protein.

Summary of Necropsy. (P.M. 545, 1928.)

Plaques (up to 0.2 cm. thick) of pinkish white firm granular secondary growth scattered over outer surface of dura especially in frontal and temporal regions causing focal, shallow, worm-eaten erosions of inner surface of skull. Layer (less than 0.05 cm. thick) of pink and red organizing clot, showing distinct leashes of capillaries, on inner surface of dura covering both cerebral convexities, especially left (fig. 5). No visible growth in leptomeninges or in substance of brain. Infiltration with firm white secondary growth (up to 0.6 cm. thick) of both temporal muscles near origin. Solid acinar and trabecular large polygonal-celled carcinoma surrounding first branch of bronchus to upper lobe of right lung. Secondary carcinomatosis of bronchial, mediastinal, lumbar, gastro-coronary, right supraclavicular and right axillary lymph-glands; of both suprarenal bodies, marrow of right femur, vertebræ, ribs and sternum. Thin sheet (up to 0.4 cm. thick) of infiltration by secondary growth in origin of vastus internus from right femur.

Great œdema and congestion of right lung and of lower lobe of left lung. Slight purulent bronchitis of right lung and of upper lobe of left lung. Collapse of posterior part of right lung and of postero-inferior fringe of upper lobe of left lung. Slightly turbid yellow effusion (60 c.c. each side) in both pleural sacs. Severe parenchymatous degeneration of myocardium. Slight general atheroma. Fatty degeneration and slight periportal fatty infiltration of liver. Severe albuminous and slight fatty degeneration of kidneys. Myeloid reaction in pulp of enlarged spleen (17 by 12 by 5 cm.) with indistinct Malpighian bodies and trabeculæ. Mucous catarrh of stomach with numerous submucous hæmorrhages in wall of body. Healed gastro-jejunostomy stoma (2·7 cm. diam.). Linear scar (2·5 cm.) in posterior wall and lower border of first part of duodenum. Operation scar in upper right quadrant of abdominal wall. Severe gingivitis. Tartar on remaining teeth. Middle ears moist. A somewhat wasted, well-developed man.

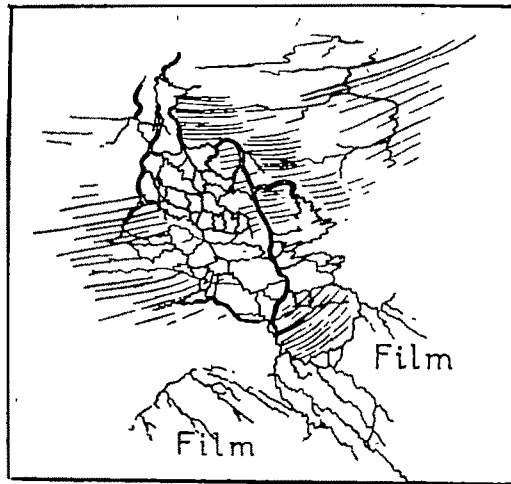


FIG. 5. Case 3.—Sketch of inner surface of dura to show engorged capillaries.

Macroscopic.—A portion of the dura from the left cerebral convexity, preserved as a museum specimen, shows conspicuous flat plaques of opaque yellowish growth on the outer surface. The inner surface is mottled: a large part is covered with conspicuous leashes of capillaries which often form an anastomosing net (fig. 5); between and over these are diffuse patches of café-au-lait gelatinous thickening. These patches do not correspond to the external plaques of growth. There are a few small nodules (up to 0·5 cm. diameter) of grey tumour-tissue projecting from the inner surface of the dura in the frontal region, the largest alongside the superior longitudinal sinus. There are many

small areas in which the inner surface of the dura presents a normal glistening appearance.

Microscopic.—*Dura*: Two pieces were selected for paraffin sections; (1) From the left parietal region with macroscopic growth on the outer surface; (2) from an unspecified site in which macroscopic growth was absent.

(1) The periosteal surface of the dura is greatly thickened by closely aggregated groups and trabeculae of polygonal tumour cells embedded in a dense collagenous matrix. This forms a layer external to the periosteal dense layer of the dura. The tumour cells frequently occupy the lumina of capillaries and veins. The infiltration does not extend diffusely into the two dense layers of the dura, but in these a large number of blood-vessels are dilated and permeated with tumour cells. The areolar layer is here little changed. It appears oedematous and the inner margin is thickened by a multiplication of spindle fibrocytes. A few red corpuscles are scattered here and there within it, but there is no gross hæmorrhage. A few of its capillaries contain plugs of tumour cells.

(2) The dura as a whole is of normal thickness. There is no diffuse infiltration of any of the layers with growth, but many veins and capillaries in the dense layers are conspicuously permeated by tumour cells mixed with fibrin thrombi. The areolar layer is thicker than normal, on account of the great distension and engorgement of its capillaries (fig. 6). In a few of these are rounded fragments of fibrin, but no tumour cells are present. The tissue about the capillaries appears oedematous and contains an excess of spindle fibroblasts. There is a little diffuse hæmorrhage, and along the inner margin is a thin zone in which spindle fibroblasts are mixed with pigment-containing macrophages.

Skull: A section of the calvaria shows groups of tumour cells in the medullary spaces.

Comment.—This case shows the earliest stage of the process of formation of subdural hæmatoma (fig. 6). Neoplastic permeation of the vessels in the two dense layers of the dura is associated with conspicuous dilatation and engorgement of the capillaries of the areolar layer. Within the areolar layer there is oedema, extravasation of red corpuscles and formation of granulation tissue.

Case 4.—*Subdural membrane.*• *Secondary sarcomatosis of dura, &c. Primary myelosarcoma (Ewing's tumour) of right iliac bone.*

A man, aged 41, had complained for eighteen weeks of pain in the right leg. Examination at first revealed only wasting of the right leg and a

moderate degree of secondary anæmia, but later a mass was felt projecting into the right side of the rectum, and X-rays showed haziness of the inner side of the right sacro-iliac joint. The patient became very weak and wasted. Nine days before death he developed weakness of the right external rectus, lateral and upward nystagmus and slight left facial weakness. The Wassermann reaction of the blood was negative.

Summary of Necropsy. (P.M. 414, 1931.)

Thin layer (up to 0·1 cm. thick) of secondary growth on inner surface and, slightly less, on outer surface of dura over all aspects of frontal, parietal and occipital regions and on basi-occipital and basi-sphenoid, with a little red and brown hæmorrhage in the inner surface of the dura. Area of focal fibrinopurulent leptomeningitis over left posterior parietal cortex. No secondary growth in brain. Primary myelosarcoma of wing of right ilium invading extensively the surrounding soft tissues, dislocating bladder and rectum to left without invasion. Secondly sarcomatous deposits in right lung, head of pancreas, and numerous deposits in marrow of femur and lumbar vertebræ. A few plaques of secondary growth on pleural aspect of left upper ribs.

Atrophy of heart. Moderate general atheroma. Subcapsular cyst, 1 cm. in diameter and containing clear fluid, in liver. Subacute inflammation and myeloid reaction in enlarged spleen (14·5 by 8·5 by 3·5 cm.). Slight dilatation of ureter, pelvis and calyces of right kidney. Edema and parenchymatous degeneration of right kidney. Congestion and parenchymatous degeneration of left kidney. Numerous fibrous adhesions over upper and middle lobes of right lung and over upper lobe and posterior border of lower lobe of left lung. Severe purulent bronchitis, great edema and considerable collapse in lower lobe of left lung. Central softening of right suprarenal body. Mucous catarrh of stomach. Colloidal hypertrophy of thyroid gland. Thymus replaced by cedematous connective tissue. Edema of brain. Middle ears clean. Extremely wasted, edentulous man.

Microscopic examination.—Two strips of dura were selected for paraffin sections. In both there is extensive infiltration of the dense and areolar layers with rounded masses of tumour cells, most of which occupy distended capillaries and veins. In places the tumour appears to spread by perivascular paths and there are more tumour cells outside the vessels than were seen in the preceding cases. Capillaries that are free from tumour are greatly engorged. The areolar layer is greatly thickened by granulation tissue and areas of diffuse hæmorrhage are present near engorged capillaries.

Comment.—In this case the spread of tumour on the inner surface of the dura was more extensive than in the previous cases and the subdural

hæmatoma was very inconspicuous, but histological sections show that the process is essentially the same as in previous cases.

There are in the records three other cases that probably belong to the same category as those just described, but suitable histological preparations are lacking and consequently they do not further our inquiry. In one (P.M. 234, 1914), in a female, aged 52, secondary sarcomatous deposits were present in the skull and one large nodule in the bone and dura on the right side lay immediately outside a "mass of black ante-mortem clot in the subdural space" over the right frontal and parietal lobes; beneath the clot the leptomeninges were stained brown and the brain was compressed. It is probable that this case was analogous to our Case 2. In two further cases slight pachymeningitis interna hæmorrhagica is described.

DISCUSSION.

The association of subdural hæmatoma and malignant disease of the dura does not appear to have been widely recognized. It was reported by Westenhoeffer (1904) in a case of carcinoma of the stomach complicated by fibrino-purulent leptomeningitis due to coliform bacilli. He observed that the capillaries in the false membrane were wide and were often plugged with cancer cells, and concluded that the formation of the membrane was more recent than the dissemination of growth. The term "pachymeningitis hæmorrhagica carcinomatosa" occurs also in the post-mortem summary of Case 49 in Pürckhauer's paper (1929) on carcinoma of the prostate. Wohlwill (1913) alludes, without further comment or description, to two examples of this combination in a series of thirty-two cases of pachymeningitis interna hæmorrhagica; the primary tumours were situated in the breast and penis respectively. The association of the two conditions is not of clinical importance, though doubtless knowledge of its occurrence will enable the observer to explain the manner of death in some cases of malignant disease of the skull and dura. What is of importance is that this association affords an opportunity for studying the histogenesis of subdural hæmatoma, which may be seen here in its earliest stages, death being due to other causes. In our four cases the subdural hæmatoma varied from a thin patchy membrane on the inner surface of the dura to a thick, more extensive membrane that merged with a mass of blood-clot (Case 2). In this case there was also a collection of 60 c.c. of old blood. Owing to an unfortunate error in technique it was impossible to tell whether

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this fluid blood lay within the membrane or free within the subdural space.¹

Study of the microscopic appearances in this series of cases has shown that the membrane forms within the areolar layer of the dura in spite of observations at operation in Case 1. In this case when the dura was reflected there was left behind a glistening red membrane covering the arachnoid and hemisphere, similar to that seen at operations upon large traumatic and idiopathic subdural hæmatomas. But histological examination showed that the membrane, though tending to be detached so easily from the overlying dense dura, was actually nothing more than a greatly thickened areolar layer of the dura.

The formation of the membrane is intimately associated with neoplastic permeation of the capillaries and veins of the dura.

From observations in Case 3 it appears that the earliest change in the production of the membrane is great dilatation and engorgement of the capillaries in the areolar layer while the veins in the dense layers of the dura contain masses of tumour cells (fig. 6). Such an engorgement is associated with cedema and is followed by rupture of capillaries and diffuse extravasation of blood both into the areolar layer and also in greater or less amount into the subdural space. A reactive process then sets in within the areolar layer and a very vascular granulation tissue is formed. There is proliferation of fibroblasts and sprouting of capillaries, while macrophages appear and later become laden with pigment. A few neutrophil leucocytes and lymphocytes are also present in places. With repeated hæmorrhages the areolar layer becomes progressively thicker. In these later stages there is also a conspicuous plugging of capillaries in the areolar layer with growth; tumour cells may be present in groups outside the vessel walls, but it is particularly emphasized that permeation of vessels in the dense layers of the dura is the constant and important histological feature. In many of these vessels fibrinous thrombosis and organization occur.

There is no evidence that the process is excited by the presence of tumour cells in the areolar layer. The membrane is sometimes found in areas where the tumour cells are restricted to the dense dura. Further, it is not an invariable accompaniment of métastatic neoplastic disease of the dura. In this Institute there are records of twenty-four other cases

¹ In a recent case (P.M. 91, 1934) a similar condition was found at necropsy. Thin plaques of growth were present between the vault and the dura and about 100 c.c. of fluid blood and gelatinous clot lay free within the subdural space. The primary growth was in the stomach.

of metastatic neoplastic disease of the dura in which no hæmorrhage or membrane was observed with the naked eye. In six of these a portion of dural metastasis was examined microscopically by us, and in all specimens where sufficient dura was included in the section to form an opinion there was no evidence of any change in the areolar layer. In general there was a massive infiltration of all layers of the dura, or a nodule of growth was present on the inner surface. In a few examples one or two vessels in the immediate neighbourhood showed permeation by growth, but the dural tumour was otherwise entirely extravascular. In this connection it must be recalled that the dura is sometimes involved by direct spread of a glioma from the adjacent brain. In this process the areolar layer is first affected; nevertheless, we have not yet observed an associated subdural hæmatoma or membrane in such cases.

From our studies we conclude that when the dura is involved locally by a circumscribed metastasis or diffusely by direct spread, it is unlikely that a subdural hæmatoma or membrane will also be found. The essential type of neoplastic involvement appears to be a permeation of veins and capillaries of the dense layers of the dura, the tumour having spread to these vessels from the overlying skull. The formation of a subdural membrane or hæmatoma in the areolar layer is the consequence of circulatory disturbance produced in the dura by this permeation.

This notion that subdural membrane and hæmatoma in these cases is produced by mechanical disturbance of the circulation of the dura receives support from the anatomical studies of Ford Robertson (1900) and Charpy (1921). These workers have shown that in the areolar layer immediately adjacent to the endothelium lining the subdural space there is a rich network of large capillaries with ampullary dilatations. These drain outwards into a second plexus in the dense dura, and thence either to the periosteum of the calvaria or to veins that accompany the main meningeal arteries. It is therefore clear that obstruction of the veins in the outer dense layers of the dura will produce dilatation of the capillaries in the inner areolar layer. These capillaries are poorly supported on the side that abuts upon the subdural space, especially when the intracranial pressure is low. It is very probable that the formation of subdural hæmatoma depends to a considerable extent on these peculiar anatomical features of the areolar layer. We have found that in the normal subject the capillaries of the areolar layer are usually empty and collapsed. They are not visible to the naked eye and are seen in histological preparations as clumps of endothelial cells. What

is described by Putnam (1925) as "a growth of capillaries" into the inner layer of the dura in chronic subdural hæmatoma may well be, at least at its beginning, a dilatation of pre-existing normal channels.

We conclude that, in the cases described, the subdural false membrane was the result of mechanical interference with the circulation by permeation of veins and capillaries with growth. The fibroblastic reaction in the areolar layer appeared to be caused by congestion of capillaries, œdema and hæmorrhage. Cases 2 and 3 suggest that the reaction may be initiated by congestion and œdema, but a survey of the material as a whole indicates that hæmorrhage plays the most important part.

A comparison of our cases with examples of pachymeningitis interna hæmorrhagica, some with a history of trauma, others complicating infections such as subacute streptococcal endocarditis, streptococcal septicæmia, pneumonia and syphilis, shows that the histological changes in the areolar layer are similar in all. In none of those that complicate infections is there a histological reaction characteristic of the associated infection. This suggests that vascular changes leading to hæmorrhage are the essential cause of this condition, whatever may be the associated pathological state.

SUMMARY.

(1) Four cases of metastatic neoplastic infiltration of the dura associated with subdural false membrane or hæmatoma are described.

(2) In these cases the subdural false membrane or hæmatoma was formed in the areolar layer of the dura. It was a consequence of dilatation, engorgement and rupture of the capillaries of the areolar layer.

(3) These changes were the result of permeation by growth of the veins and capillaries of the outer dense layers of the dura.

(4) The subdural membrane or hæmatoma was histologically identical with idiopathic "pachymeningitis hæmorrhagica interna" and traumatic subdural hæmatoma.

(5) Subdural false membrane or hæmatoma can be produced entirely by obstruction of the circulation of the dura.

ACKNOWLEDGMENTS.

We desire to thank Professor H. M. Turnbull for his help in the preparation of this paper, and Dr. T. G. Reah for assistance in identifying cases in the post-mortem records of former years. The cost of

microphotographs was defrayed by the Charles Bingham Bolton Fund for Neurology.

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PLATE I.

FIG. 2. *Case 1.*—Dura and membrane from posterior part of decompression area. (c) inner and outer dense layers of dura; (A) greatly thickened areolar layer. Rounded dark areas in both layers are vessels filled with growth. Hæmatoxylin and eosin. $\times 28$.

FIG. 3.—Magnified portion of FIG. 2 to show permeation by growth of vessels in inner dense (c) and areolar (A) layers of dura. $\times 95$.

FIG. 4. *Case 2.*—Section of dura showing thickening of areolar layer (A) and permeation by growth of vessels in inner part of dense layers (c) and in areolar layer. Hæmatoxylin and eosin. $\times 52$.

FIG. 6. *Case 3.*—Section of dura showing permeation by growth of vessels in dense layers (c) and great distension of capillaries in areolar layer (A). Hæmatoxylin and eosin. $\times 78$.

PLATE I.

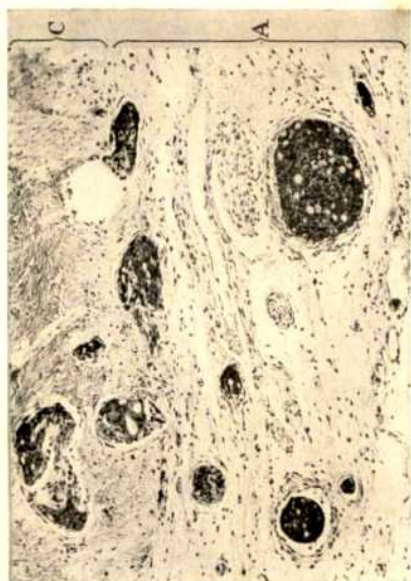


FIG. 3.



FIG. 6.



FIG. 2.



FIG. 4.

To illustrate paper by Dorothy S. Russell and Hugh Cairns.

HOUR-GLASS OR DUMB-BELL TUMOURS OF THE SPINE.

BY HENRY COHEN.

Royal Infirmary, Liverpool.

IN a series of forty-two cases of compression paraplegia due to tumours of the spine or spinal cord, three cases of so-called hour-glass or dumb-bell tumours have been encountered. No direct reference to these curiously shaped tumours occurs in the literature of this country, and as they are not so uncommon as the absence of a collected series would indicate, I venture to report them. They merit separate clinical description because despite their varied pathology, they display characteristic features which give rise to special problems, both in diagnosis and treatment.

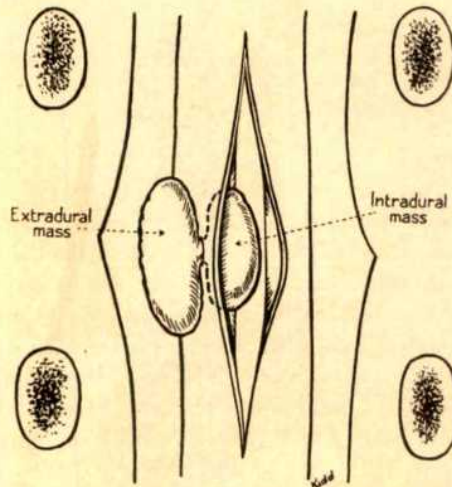


FIG. 1.—Showing diagrammatically an hour-glass tumour wholly intraspinal with connecting stalk passing through dura mater.

Two types of hour-glass tumour in this region have been described:—

(1) Wholly intraspinal, but both extra- and intradural masses are connected by a narrow pedicle (fig. 1). These offer no special problem in diagnosis, but if only extradural exposure is made at operation and the pedicle not observed, the intradural mass, the main factor in compression, may be overlooked.

(2) Those having extra- and intra-dural masses joined by a narrow pedicle passing through an enlarged intervertebral foramen (fig. 2); very rarely the site of the pedicle is interlaminal; in rare instances the intraspinal portion may be again constricted as it penetrates the dura.

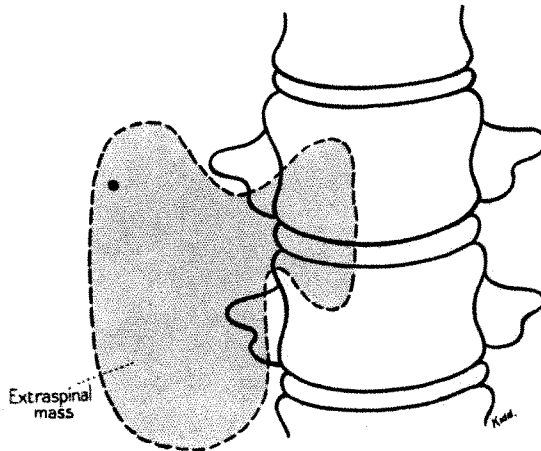


FIG. 2.—Showing diagrammatically an hour-glass tumour with extra- and intra-spinal portions connected by stalk passing through the intervertebral foramen.

SUMMARY OF CASE RECORDS.

Case 1.—Mrs. H., aged 27, complained of aching in left lumbar region on exertion, associated with weakness of left lower limb. Pain first appeared four years ago after her confinement; it gradually increased in severity during the next six months, when after X-ray examination tuberculous disease of the spine was diagnosed. She was kept on a frame for six months but no improvement resulted and in December 1930, after consultation with Sir Robert Jones, a spinal support was worn, with considerable improvement.

On December 23, 1931, clinical examination revealed motor and sensory changes in the distribution of the left second, third and fourth lumbar nerves; no tumour could be palpated in the left lumbar area. The radiogram taken on this day showed the characteristic changes of an hour-glass tumour of the spine (figs. 3 and 4). Three weeks later loss of power in both lower limbs with urinary incontinence and difficult defæcation developed.

Operation (February 6, 1932) by Mr. T. P. McMurray. A tumour encountered in the paravertebral muscles; laminectomy was performed. As the tumour intimately mingled with the cauda equina complete removal was impossible, but pressure was relieved. Pathological report showed the growth to be a fibroblastoma.

She was advised to continue wearing the spinal support, and after the operation she improved considerably. Her doctor reports April 28, 1933,

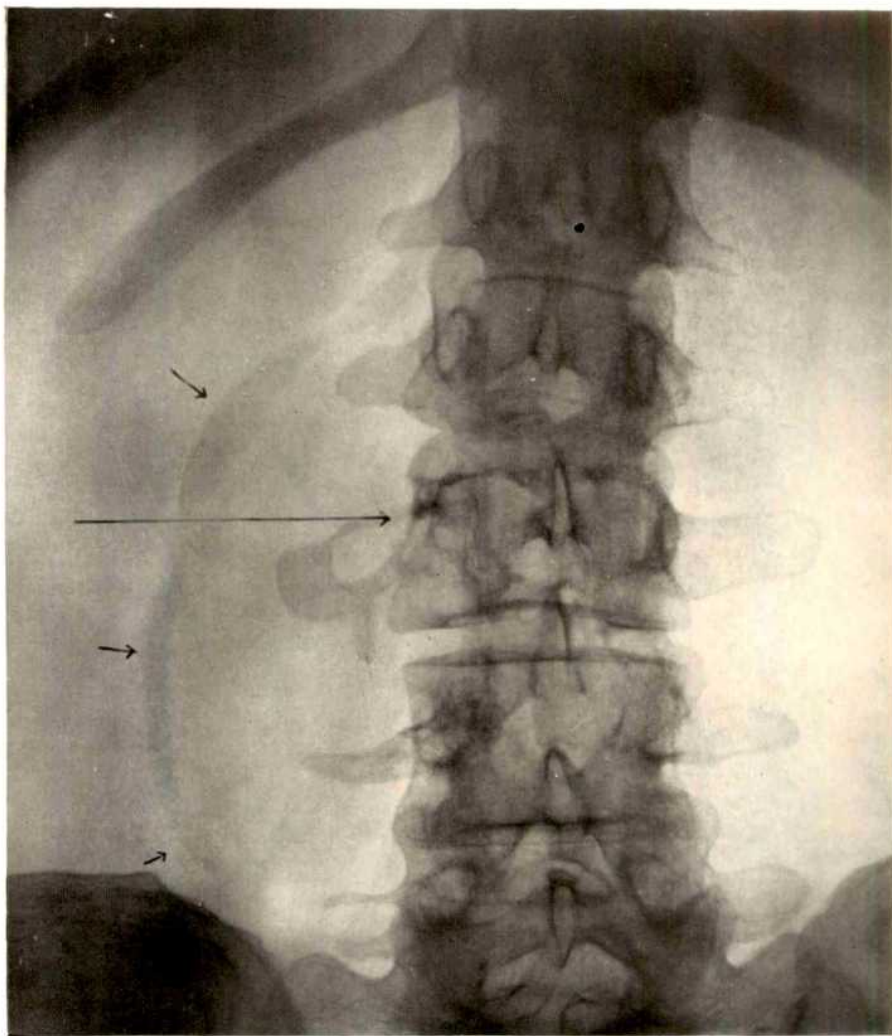


FIG. 3 (*Case 1*).—Antero-posterior radiogram of the spine showing outline of extraspinal mass (small arrows) and erosion of the bone (large arrow).

To illustrate paper by Henry Cohen.

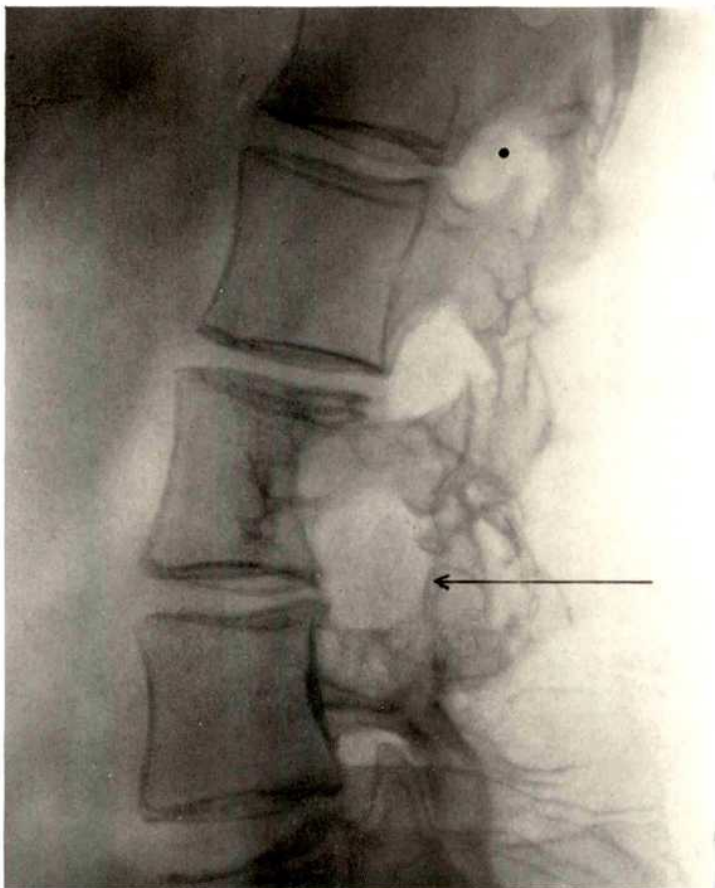


FIG. 4 (*Case 1*).—Lateral radiogram showing characteristic enlargement of left intervertebral foramen between 3rd and 4th lumbar vertebrae, caused by pedicle connecting the two masses.

To illustrate paper by Henry Cohen.

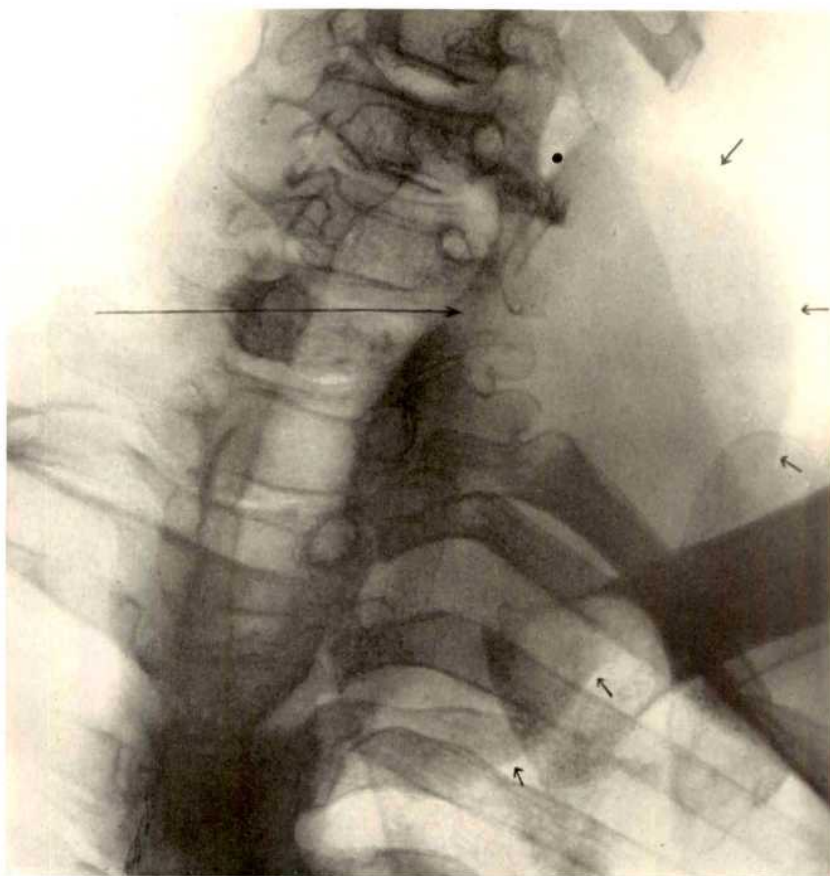


FIG. 5 (*Case 2*).—Antero-posterior radiogram of the spine showing outline of extraspinal mass (small arrows) and bone erosion (large arrow).

To illustrate paper by Henry Cohen.

"She has not required any treatment whatsoever since the operation, having enjoyed good health; her back is still in splints and generally she is very comfortable: if she over-exerts herself she gets what she describes as a tired feeling in her back; on one or two occasions she has complained of severe pain in the back and these periods have coincided with the menses. If she leaves off the support, however, her pain returns. She expresses herself as being in very good health."

Case 2.—R. S. H., male, aged 37, was first seen June 14, 1932. He first complained of severe pains radiating down the inner side of the right arm which gradually increased in severity and extent; in 1927, drooping of the right upper eyelid was observed; in 1932, a movable hard lump appeared in the right lower cervical area, and operation was undertaken on the suspicion that the swelling was glandular in origin. A chocolate-coloured grumous material was evacuated and the condition described as a "cystic hæmatoma." Symptoms persisted, and in June 1932, the cervical spine was X-rayed and reported on as follows (fig. 5): "The right halves of the bodies of the sixth and seventh cervical vertebræ showed destructive changes. Extending out from this area into the right supraclavicular (and to a slight extent retroclavicular) region is a homogeneous shadow with well-defined rounded borders. The trachea is displaced slightly towards the left side and very slightly forwards. The X-ray appearances are those of tuberculous disease involving the right half of the body of the seventh cervical vertebra and to a less extent of the sixth cervical vertebra, with the formation of a cold abscess in the right side of the neck."

Clinical examination revealed a fixed, firm, non-fluctuating mass in the right supraclavicular area; wasting of the intrinsic muscles of the right hand and sensory change indicating involvement of the first dorsal nerve, and evidence of a Brown-Séquard syndrome due to pressure on the right side of the spinal cord. Flexion of the head produced constant pain in the left mammary area.

Operation (June 30, 1932) by Professor R. E. Kelly. The mass was exposed from the back after removing the posterior portions of the first and second ribs; it invaded the lower cord of the brachial plexus and contained chocolate-coloured pultaceous material though most of the tumour was firm. The patient died six hours later.

The autopsy was limited to site of operation. No visible secondaries were found. The tumour, which was black, soft and friable, lay on the right side of the vertebral column extending up to the sixth cervical and down to the upper border of the fourth thoracic vertebra. The main mass of the tumour lay on the ventral surface of the first and second ribs, but it entered the spinal canal between the seventh cervical and first thoracic vertebræ, and also between the first and second thoracic vertebræ. The spinal dura was involved on its outer anterolateral surface and the cord was displaced to the left. On opening the dura from behind there appeared to be no extension of the growth intradurally. There was local invasion by the growth in the vertebral laminae, muscles, and the pleura and lung at the right apex; the posterior and inner cords of the brachial plexus were also involved in the tumour mass.

Histology (fig. 6).—The tumour cells are large and mainly ovoid; they are densely packed with a brown pigment (melanin). The nucleus stains deeply with hæmatoxylin in most of the cells, but in many the structure of the cell is completely obscured by the pigment. It is impossible to obtain a clear picture of either cell or tissue architecture for this reason. The invasive character of the tumour is best seen in sections taken from the outlying portions of the growth (e.g., pleura) in which are isolated clumps of pigmented cells separated by a fibrous stroma. Pieces removed from the centre of the growth show areas of necrosis with a scattering of the pigment outside the degenerated cells.

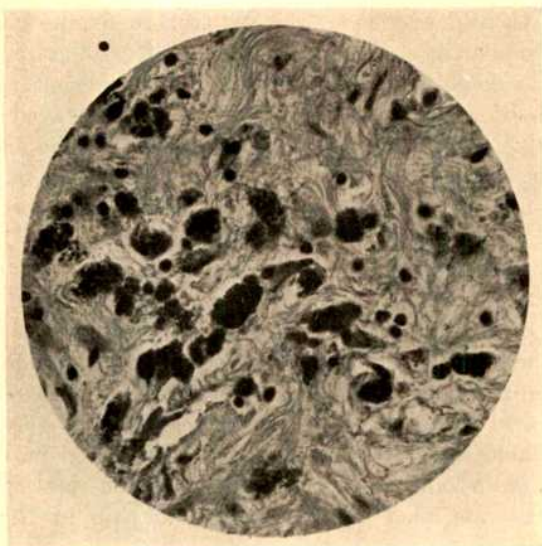


FIG. 6 (Case 2).—Section taken from the periphery of the growth ($\times 300$).

This tumour may have arisen as an extradural spinal tumour growing out of the canal, or it may have arisen from without, possibly from the inferior cervical or first thoracic sympathetic ganglion which lies somewhere within the main mass of the tumour.

Case 3.—A. B., male, aged 21, was seen January 14, 1931. He had complained of weakness and numbness of both lower limbs and of the left arm for six months. For three years he suffered from "rheumatic" pain radiating from the left shoulder down the outer side of the arm; gradually weakness of the left arm developed, and six months ago numbness in the right leg with an inability to appreciate cold water over the right leg; gradually progressive difficulty in walking appeared.

On examination there was evidence of compression at level of seventh cervical and first dorsal segments of the cord, affecting the left side. Cerebrospinal manometry showed evidence of partial obstruction. The cerebrospinal

fluid contained a slight excess of protein, but no other change. X-ray of the cervical and dorsal spines revealed no abnormality. The Wassermann reaction in the blood was negative.

Operation (25.1.31) by Professor R. E. Kelly. On incising the dura, a tumour $1 \times \frac{1}{2}$ inch presented on the left side of the cord underlying the posterior root of the sixth cervical nerve which was cut to facilitate its removal; on raising the tumour it was found to extend along the intervertebral foramen, and this necessitated removal of more bone and dura; then the tumour was found to be passing outside the spine. After its removal by morcelllement the bed of the tumour was represented by a cavity about the

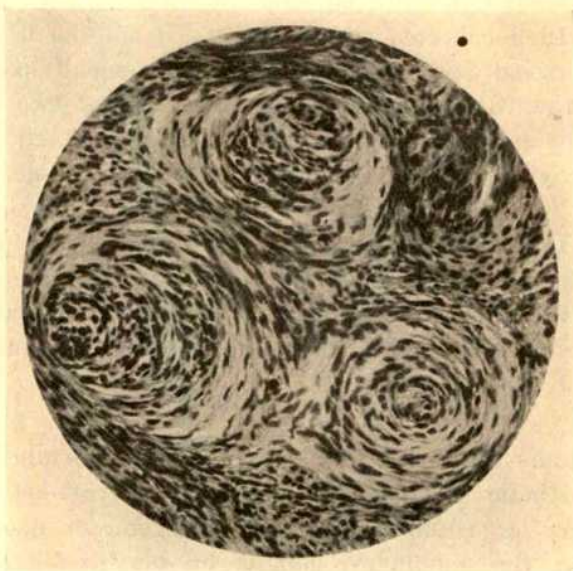


FIG. 7 (Case 3).—Section of the tumour ($\times 250$).

size of a walnut extending outside the intervertebral foramen; this cavity was scraped and the area treated by coagulation with electrocautery.

Pathological report.—"Meningeal endothelioma of the cord" (fig. 7). The patient made a complete recovery, except for slight sensory disturbance in left upper limb which has persisted until the present.

SITE OF TUMOURS.

Any level of the spine may be implicated and these tumours may arise from any structure, nervous, fascial, osseous, &c. They may arise intraspinally and grow outwards through an intervertebral foramen or rarely between the laminae, thus forming an extraspinal portion, or they may arise extraspinally and then extend through an intervertebral

foramen and form the intraspinal prolongation. The communicating narrowed isthmus gives the hour-glass or dumb-bell shape; usually the intervertebral foramen through which the tumour passes is enlarged by pressure atrophy; occasionally invasion and destruction of bone occur. It is customary to exclude from the group under discussion rapidly growing malignant tumours which cause gross vertebral destruction by direct infiltration and invade the cord secondarily.

LITERATURE.

There is scant reference in the literature to these tumours. Heuer [1] in 1929 collected sixty-one cases from the literature, and added three personally observed cases and two personally communicated cases. Since then Gonzalez-Aguilar [2] has reported two round-celled sarcomas of the hour-glass type in the dorsal region, and Guleke [3] reports one cervical (chondroma) and one lumbar ("sympaticoblastoma").

In 1933 a further fifteen cases were added to the literature by Naffziger and Brown [4] bringing the total recorded cases up to eighty-five. Many of these have not been labelled hour-glass tumours, but the descriptions given in the records leave no doubt of their nature. They probably occur with far greater frequency than the literature indicates.

PATHOLOGY.

These tumours may arise from any tissue—the membranes, nerves, ganglia, sympathetic nervous system, ligaments, cartilage, bone, fat, &c.—but a very large number are fibroblastogenic or neurogenic and originate from the meninges, ganglia or nerve-roots. The great majority are benign encapsulated growths though a few are definitely malignant.

Pathogenesis.—Why these tumours should assume an hour-glass shape has been the subject of much discussion. If they arose primarily either intra- or extra-spinally, or even in the intervertebral foramen itself, and spread outwards or inwards, their shape could be explained, but it is difficult to understand why tumours originally extra- or intra-spinal should follow this line of growth except in the case of those arising from the nerve-sheath. Foyer discusses Coenen's view that these tumours are determined early in the course of development, and that they assume their hour-glass shape because other structures grow round and constrict them, the pathogenesis being similar to spina bifida occulta, dermoid cysts with both intra- and extra-cranial portions, intra- and extra-thoracic lipomata, &c.

Symptomatology.—The usual symptomatology of spinal compression with the accompanying changes in pressure and chemistry of the cerebrospinal fluid may be present, but additional features which merit emphasis are :—

(1) The frequent and severe root pain, resulting from the situation of the tumour.

(2) In the cervical region and occasionally in the lumbar region a palpable lump may be found : in the latter area, either in the back or on abdominal examination. Rarely except by X-ray examination is the extraspinal portion in a thoracic site discovered.

(3) Symptoms may arise from vertebral damage, i.e. pain on movement, rigidity, &c.

Diagnosis.—Acquaintance with the lesion is the prime essential for its recognition. Most cases, particularly those with vertebral damage demonstrated by X-ray examination, have been regarded as tuberculous disease of the spine with secondary abscess formation, an error only possible if an hour-glass tumour of the spine has not previously been seen by the physician or radiologist.

Treatment.—In order to prevent recurrence of the tumour, both intra- and extra-spinal portions must be removed. Many cases of recurrence of spinal tumours depend upon a non-recognition of the extraspinal portion in this type of case. Some surgeons advocate one, others a two-stage operation, but all seem agreed that the primary attack should be on the intraspinal portion. It is interesting to note that in the case of a thoracic situation the extraspinal portion has been so large that it has been removed without recognizing its hour-glass nature ; as a result, not only has compression paraplegia developed subsequently but injury to the spinal meninges has occurred during the removal of the extraspinal portion so that cerebrospinal fluid has leaked into the pleura and produced a hydrothorax.

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THE CEREBROSPINAL FLUID IN MULTIPLE SCLEROSIS.

BY H. HOUSTON MERRITT, M.D.

(From the Neurological Unit, Boston City Hospital, the Cerebrospinal Fluid Laboratory, Massachusetts General Hospital, and the Department of Neuropathology, Harvard Medical School, Boston, Mass.)

THE purpose of this article is to report the cerebrospinal fluid findings in 152 fluids from 100 cases of multiple sclerosis that have been under observation on the Neurological Services of the Boston City Hospital and the Massachusetts General Hospital during the past nine years and to summarize the reports in the literature on this subject.

I.—CEREBROSPINAL FLUID FINDINGS IN 100 CASES OF MULTIPLE SCLEROSIS.

The 100 cases here reported are all fairly typical cases. They have all been examined by several observers who have concurred in the diagnosis. All cases were excluded in which the diagnosis was doubtful, or in which there was a difference of opinion among various observers. The Wassermann test was done on the blood and cerebrospinal fluid, and was negative in every case.

Necropsy confirmation had been obtained in only one of the cases, but it is felt that the diagnosis is relatively certain in the remainder of the cases. In a disease with protean manifestations 100 per cent. accuracy of diagnosis is hardly possible, and it is likely that we have excluded some cases that would show the typical pathology, and on the other hand we may have included some in which the diagnosis would not be confirmed by necropsy. We have, however, tried to err on the side of conservatism.

(1) *Cerebrospinal fluid pressure*.—The cerebrospinal fluid pressure was measured 123 times in the 100 cases. Lumbar puncture was performed with the patient in the lateral recumbent position. The cerebrospinal fluid pressure was measured with the Fremont-Smith modification of the Ayer manometer. The pressures ranged between 40 and 220 mm., with an average of 131 mm. of cerebrospinal fluid pressure. In only one instance was the pressure more than 200 mm.

of cerebrospinal fluid. The dynamics of the cerebrospinal fluid circulation, as tested by compression of the jugular veins, &c., was normal in all instances. Table I gives an analysis of the pressure at 123 punctures.

TABLE I.—THE CEREBROSPINAL FLUID PRESSURE IN 100 CASES OF MULTIPLE SCLEROSIS (123 PUNCTURES).

Cerebrospinal fluid pressure (in mm. of C.S.F.)		Number of punctures		Percentage
Under 80	..	15	..	12
81-150	..	78	..	63
151-180	..	24	..	20
181-200	..	5	..	4
201-220	..	1	..	1
		123	..	100

(2) *Cells*.—The cells in the spinal fluid were counted in ordinary blood-counting chambers, the cells being faintly stained with Unna's polychrome methylene blue (methylthionine chloride, U.S.P.) The cell-counts varied between 0 and 40 per c.mm., with an average of 6 per c.mm. Table II gives an analysis of the findings in the 141 fluids in which the cells were counted.

TABLE II.—ANALYSIS OF THE CELL COUNT IN 141 FLUIDS.

Cells per c.mm.		Number of cases		Number of fluids
Not counted	..	4	..	—
0	..	8	..	18
1-5	..	54	..	79
6-10	..	14	..	20
11-20	..	12	..	14
21-40	..	8	..	10
Total	..	100	..	141

Sixty-nine per cent. of the 141 fluids in which the cells were counted had less than six cells per c.mm. and 31 per cent. had six or more cells per c.mm. More than ten cells per c.mm. were found in 18 per cent. The cells were chiefly small lymphocytes. Occasionally small mononuclear cells were found. Polymorphonuclear leucocytes were not found.

(3) *Protein content*.—The protein content was determined in 151 fluids from 100 cases according to Ayer, Dailey and Fremont-Smith [1] modification of the Denis and Denis and Ayer method. Their figure of 45 mg. per 100 c.c. is considered as the upper limit of normal values. Our results varied between 13 mg. and 133 mg., with an average of 43 mg. per 100 c.c. The protein content was over 100 mg. in only three cases (4 fluids). Sixty-eight per cent. of the fluids showed a total protein content within normal limits. Forty per cent. of the fluids

with a normal protein had a protein content between 36 to 45 m.g., i.e. high normal values. Thirty-two per cent. of the fluids showed an increase in the total protein content. In 9 per cent. of the fluids, the protein content was over 75 mg. per 100 c.c. Table III gives a summary of the findings.

TABLE III.—ANALYSIS OF THE PROTEIN CONTENT IN 151 FLUIDS.

Protein mg. per 100 c.c.		Number of cases		Number of fluids
Less than 20	..	5	..	7
21-35	..	32	..	55
36-45	..	25	..	40
46-75	..	28	..	36
76-100	..	7	..	9
Over 100	..	8	..	4
		100	..	151

A qualitative globulin test was done in 75 fluids and was positive in 38 instances or 51 per cent. The Pandy test for globulin was done in 52 fluids and was positive 31 times. The test was usually only slightly positive. The total protein content was normal in 18 of the 31 fluids giving a positive Pandy test. The Ross-Jones test for globulin was done in 35 fluids and was positive 8 times. The total protein content was normal in 3 of these 8 fluids.

(4) *Sugar content*.—The reducing substances were determined in 31 fluids by the Folin-Wu method as modified by Rothberg and Evans [2]. The results varied between 51 and 78 mg. per 100 c.c. with an average of 66 mg. per 100 c.c. (normal values 45 to 93 mg. per 100 c.c. [3]).

(5) *Chloride content*.—The chloride content was determined in 26 fluids by the Wilson-Ball [4] modification of the Van Slyke method. The results (expressed in mg. of NaCl per 100 c.c.) varied from 684 to 754 mg. with an average of 724 mg. per 100 c.c. In only one fluid was the chloride content below 695 mg. per 100 c.c. (normal values 695 to 750 mg. per 100 c.c. [3]).

(6) *Non-protein nitrogen*.—The non-protein nitrogen was determined in 8 fluids by the Folin-Wu [5] method. The results varied from 13 to 28 mg. with an average of 17 mg. per 100 c.c. (normal values 12 to 28 mg. per 100 c.c. [3]).

(7) *Colloidal gold reaction*.—The colloidal gold reaction was done according to the method of Lange as described by Cockrill [6] in 142 fluids (Table IV). The results varied from a strong first zone curve ("paretic") to an entirely negative test. The expression "strong curve" is used to represent one in which certain tubes showed a complete

decolorization, 5, or a blue colour, 4. "Weak curves" mean those curves in which the maximum colour change is violet, 3. Where the maximum colour change was lilac, 2, the fluid was classified as slightly abnormal. Any change in the colloidal gold solution of a lesser degree was considered as normal.

TABLE IV.—ANALYSIS OF THE COLLOIDAL GOLD REACTION ON 142 FLUIDS.

	Number of cases		Number of fluids		Percentage of fluids
Strong first zone curve ..	28	..	88	..	27
Weak " " " " ..	6	..	8	..	6
Strong mid-zone curve ..	4	..	4	..	8
Weak " " " " ..	17	..	20	..	14
Slightly abnormal curve ..	23	..	36	..	25
Normal ..	24	..	36	..	25
Not done ..	3	..	—	..	—
	100	..	142	..	100

Thirty-three per cent. of the fluids gave a first zone curve, 27 per cent. of which were strong, 6 per cent. weak. Seventeen per cent. of the fluids gave a mid-zone curve of which 3 per cent. were strong and 14 per cent. were weak. In 25 per cent. the gold curve was only slightly abnormal (lilac colour change) and in 25 per cent. the curve was normal.

(8) *Calcium*.—The calcium content of the serum and the cerebrospinal fluid was determined in 15 cases by the method of Fiske and Logan [7]. In all cases the cerebrospinal fluid calcium was between 47 and 55 per cent. of the blood calcium level. The actual range of figures was 4.2 to 5.0 mg. with an average of 4.8 mg. for the cerebrospinal fluid and 9.3 to 10 mg. with an average of 9.6 mg. per 100 c.c. for the serum calcium content. (Normal cerebrospinal fluid values 4.1 to 5.9 mg. per 100 c.c. [3]).

(9) *Phosphorus*.—The inorganic phosphorus content of the serum and cerebrospinal fluids was determined in 7 cases by the method of Fiske and Subbarow [8]. The cerebrospinal fluid content results varied between 1.2 and 1.6 mg. with an average of 1.4 mg. per 100 c.c. The serum phosphorus content varied between 2.9 and 4.5 mg., with an average of 3.8 mg. per 100 c.c. (normal values for cerebrospinal fluid 1.2 to 2 mg. per 100 c.c. [3]).

(10) *Sodium*.—The sodium content was determined in 12 fluids by the Rourke [9] modification of the Kramer-Gittleman method. Our results varied from 297 to 343 mg. with an average of 326 mg. per 100 c.c. (normal values 297 to 348 mg. per 100 c.c. [3]).

(11) *Total solids*.—The total solids of the cerebrospinal fluids were determined in 18 fluids by drying to a constant weight at from 105° to 110° C. The results varied from 0.85 to 1.21 per cent. with an average of 1.0 per cent. (Normal values 0.85 to 1.70 per cent. [3]).

(12) *Freezing point*.—The freezing point was determined in 9 cases by the method of Beckmann [10], a Heidenhain thermometer being used. The results varied between -0.540°C. and -0.580°C. with an average of -0.572°C. (Normal values -0.540°C. to -603°C. [3]).

DISCUSSION.

From our findings it appears that abnormalities in the cerebrospinal fluid in multiple sclerosis are almost entirely limited to an increase in cells, an increase in protein, and changes in the colloidal gold reaction. The pressure, hydro-dynamics, sugar, non-protein nitrogen, chlorides, sodium, calcium, phosphorus, total solid content and freezing point are nearly always normal.

The cerebrospinal fluid in this disease may vary from an entirely normal fluid to a fluid showing increase in cells up to 40 per c.mm., a positive globulin reaction, a total protein increase up to 133 mg. per 100 c.c. and a change in the colloidal gold reaction in the first or mid-zone up to a strong "paretic curve." Abnormalities in one or two of these reactions is considerably more common than in all three.

If each individual test is considered it is seen that normal findings occurred in the following percentages: cells, 69 per cent; protein, 68 per cent.; and colloidal gold curve 25 per cent. If, however, the cases are analysed for all three tests it is apparent that only a very small percentage (17 per cent.) gave entirely normal findings. This is especially true when the patients had more than one lumbar puncture. In several cases the fluid obtained on subsequent punctures showed variations from the findings at the first puncture. In this connection it is of interest that Fremont-Smith, Putnam and Cobb [11] found that the cell-count and protein content of the cerebrospinal fluid from cases of multiple sclerosis occasionally showed a marked increase during "forced drainage."

Table V shows the relative incidence of the abnormalities in cell-count, protein content, and colloidal gold reaction in our cases. In the cases which had two or more punctures a composite of all the fluids was used in determining the percentages of abnormalities. The fluids were entirely normal in only 17 cases. One abnormality was present in 37 cases and more than one abnormality was present in 46 cases. An

abnormality in all three, i.e. pleocytosis, increased protein and an abnormal gold curve was found in only 14 cases.

TABLE V.—RELATIVE FREQUENCY OF ABNORMALITIES IN THE CEREBROSPINAL FLUID.

	Number of cases			
All fluids normal	..	..	..	17
Pleocytosis only	..	..	..	1
Increased total protein only	..	..	..	7
Slightly abnormal gold curve only	..	..	..	13
First zone or mid-zone gold curve only	..	..	..	16
Abnormalities in two tests	..	..	..	32
Abnormalities in all three tests.. .. .	..	..	..	14
Total	..	..	..	100

The presence of a strong zone I (paretic) colloidal gold curve in 13 fluids which had neither a pleocytosis nor abnormal protein content shows that this reaction is not dependent on either of these two constituents. Our data also shows that a normal or only slightly abnormal colloidal gold reaction may be found in cases with a high protein content. Nine of the 13 fluids with a protein content greater than 75 mg. had a normal or only slightly abnormal gold curve.

An entirely normal gold curve was not found in any of the fluids with more than 10 cells per c.mm. There were 24 fluids with more than 10 cells per c.mm., 11 showed a zone I, 8 a mid-zone and 5 a slightly abnormal colloidal gold curve. A marked change in the colloidal gold curve (zone I or mid-zone) was therefore found in only 31 per cent. of the fluids with a protein content greater than 75 mg. per 100 c.c. as compared to 79 per cent. of the fluids with more than 10 cells per c.mm.

There was no definite relationship between the cell count and protein content of the fluids. Fourteen (60 per cent.) of the 24 fluids with more than 10 cells per c.mm. had normal protein content. Only one of the 13 fluids with a protein content greater than 75 mg. had a cell-count greater than 5 per c.mm., and in none of these fluids was the cell-count greater than 10 per c.mm.

THE RELATIONSHIP OF THE CEREBROSPINAL FLUID FINDINGS TO THE CLINICAL COURSE.

In a disease such as multiple sclerosis it is impossible definitely to divide the cases into progressive and stationary ones; cases presenting new symptoms are easily classified but it is very difficult to determine from the records whether old symptoms are progressing. It is questionable, therefore, if such an analysis will yield reliable results. Neverthe-

less, we have attempted to divide the cases into two groups: progressive and stationary. In the latter group we placed all the cases that have had no new symptom for one year, and in whom there had been no definite progression of the old symptoms within the year previous to the lumbar puncture. All other cases are, for the purpose of comparison, classified as progressive, although in eight cases the patients were under observation too short an interval after their initial attack to classify them satisfactorily.

With the above criteria 18 of the 100 cases could be classed as stationary. Tables VI, VII and VIII present a comparison of the findings in the fluids on the progressive and stationary cases.

TABLE VI.—COMPARISON OF THE CELL COUNT IN THE FLUIDS FROM PROGRESSIVE AND STATIONARY CASES.

Cells per c.mm.		Progressive		Stationary		Total	
		Number fluids	Per cent.	Number fluids	Per cent.	Number fluids	Per cent.
Less than 6	..	75	64	22	92	97	69
6-10	..	18	16	2	8	20	14
Over 10	..	24	20	0	0	24	17
		117	100	24	100	141	100

TABLE VII.—COMPARISON OF THE PROTEIN CONTENT IN THE FLUIDS FROM PROGRESSIVE AND STATIONARY CASES.

Protein mg./100 c.c.		Progressive		Stationary		Total	
		Number fluids	Per cent.	Number fluids	Per cent.	Number fluids	Per cent.
Normal	..	82	66	20	77	102	68
Over 45	..	43	34	6	23	49	32
		125	100	26	100	151	100

TABLE VIII.—COMPARISON OF THE COLLOIDAL GOLD CURVE IN THE FLUIDS FROM PROGRESSIVE AND STATIONARY CASES.

		Progressive		Stationary		Total	
		Number fluids	Per cent.	Number fluids	Per cent.	Number fluids	Per cent.
Normal	..	22	19	14	58	36	25
Slightly abnormal	..	81	26	5	21	86	25
Zone I curve	..	43	86	3	13	46	88
Mid-zone curve	..	22	19	2	8	24	17
		118	100	24	100	142	100

While it was found that a normal or almost normal fluid could be present in a case showing new symptoms or progression of old symptoms, and also that a definitely abnormal fluid could be present in a stationary case, there was a much higher percentage of abnormal findings in the progressive cases, as shown in Table IX.

TABLE IX.—SUMMARY OF THE COMPARISON OF THE PERCENTAGE OF ABNORMAL FINDINGS IN THE PROGRESSIVE AND STATIONARY CASES.

		Progressive cases	Stationary cases
Pleocytosis more than 5 per c.mm.	..	86 per cent.	8 per cent.
Pleocytosis more than 10 per c.mm.	..	20 "	0 "
Protein more than 45 mg. per 100 c.c.	..	34 "	23 "
Abnormal colloidal gold—			
Zone I curve		36 "	13 "
Zone II curve		19 "	8 "

Two significant facts were brought out by the analysis of our cases: (1) All of the 24 fluids with a pleocytosis of over 10 cells per c.mm. were in the progressive cases. This is in accord with the findings of Ayer and Foster [12a]. Their 8 cases with a like grade of pleocytosis were progressive ones. (2) Table V indicates that 14 cases showed an abnormality in the cell-count, protein content and colloidal gold test. Twelve of these cases were progressive and the two remaining were early cases.

II.—SUMMARY OF THE CASES REPORTED IN THE LITERATURE.

Table X gives a summary of the cerebrospinal fluid findings in 1,068 cases of multiple sclerosis that are recorded in the literature [12]. Our 100 cases are included in this table.

(1) *Pressure*.—There is very little in the literature with regard to cerebrospinal fluid pressure in multiple sclerosis. Most authors state that it is generally normal. Ayer [12a] found the pressure normal in all of his 38 cases. Greenfield and Carmichael [12e] state that the pressure is commonly raised but is never over 200 mm. of cerebrospinal fluid. Guillain [12f] found the pressure elevated in 5 of his 14 cases. In our series the average pressure was 131 mm. of cerebrospinal fluid. The highest pressure recorded was 220 mm.

(2) *Cells*.—In the 986 fluids in which the cell-counts were recorded, 283 fluids or 28 per cent. showed a pleocytosis. It is agreed by most authors that 5 cells per c.mm. is the upper limit of normal and this figure was used in computing these cases whenever the data were sufficient to permit. Pleocytosis when found was generally of only a moderate degree. In the greater majority of the cases it was under 10. Greenfield and Carmichael [12e] report one case with 115 cells and Moore [12h] found 89 cells in one case, but such counts are exceptional. The upper limit of most other observers was 40 to 50 cells per c.mm.

(3) *Protein content*.—(a) *Qualitative*: In 825 qualitative tests the protein content (usually globulin) was abnormal in 374 or 45 per cent.

TABLE X.—THE CEREBROSPINAL FLUID FINDINGS IN 1,068 CASES OF MULTIPLE SCLEROSIS.

AUTHOR	Number of cases	CELLS		PROTEIN				COLLOIDAL GOLD				
		Number of counts	Number with increase	Qualitative		Quantitative		Number of tests	First zone	Mid-zone	Other forms	Neg.
				Number of tests	Number with increase	Number of tests	Number with increase					
Ayer ..	88	51	19	31	9	38	19	42	21	7	3	11
Beriel ..	47	47	11	—	—	—	—	—	—	—	—	—
Conoway ..	10	10	4	10	8	—	—	10	2	8	—	5
Ekuchen ..	41	41	21	41	28	—	—	41	10	17	—	14
Greenfield and Carmichael	260	260	80	260	86	260	29	190	27	87	118	18
Gullain ..	27	27	1	—	—	27	8	27*	1	2	14	10
Kaplan ..	18	—	—	—	—	—	—	18	1	—	—	17
Moore ..	28	28	16	28	25	—	—	28	18	8	—	7
Müller ..	100	100	27	100	49	100	33	47	7	19	10	21
Potts ..	85	—	—	—	—	—	—	85	11	4	—	10
Reys ..	67	67	28	67	21	—	—	—	—	—	—	—
Rogers ..	65	—	—	—	—	—	—	65	17	4	19	25
Sternberg ..	126	108	67	126	94	—	—	83	28	34	2	21
Warwick ..	19	19	6	—	—	—	—	19	6	2	2	10
Wexberg ..	82	83	9	82	19	—	—	77	16	20	—	41
Worster-Drought ..	15	15	—	15	2	—	—	15	1	12	—	2
Personal Cases ..	100	141	44	75	88	151	49	142	46	24	36	36
TOTAL ..	1,068	996	288	895	874	566	138	839	209	188	199	243
Per cent. abnormal ..	—	—	28%	—	45%	—	24%	—	25%	32%	24%	—

* Colloidal benzoin test.

The various tests used were generally reported as being weakly or only moderately positive.

(b) *Quantitative*: The percentage of cases showing a quantitatively increased protein content was somewhat less than that of the qualitative test. Of the 566 quantitative tests, 138 or 24 per cent. showed an increase above the arbitrary normal limit. A large percentage of the remaining fluids were stated to have high normal protein values. The protein content of the fluids varied between 150 and 13 mg. In only three of our cases was the protein over 100 mg. Greenfield and Carmichael [12e] found a total protein over 100 mg. in only one case.

(4) *Colloidal gold test*.—This test has received the most attention in the literature as it is often the most striking finding in the fluid. It is also not infrequently the only abnormality found.

In the 839 fluids in which this test has been done 209 or 25 per cent. showed a first zone (paretic) curve; 188 or 22 per cent. showed a mid-zone (luetic) curve; 199 additional cases, 24 per cent., showed slight abnormalities (lilac in the mid-zone), or other variations from the normal. Thus in 596 cases or 71 per cent. the colloidal gold curve was abnormal.

With regard to the influence of the cells and protein content on the gold curve our results were in agreement with the statement of Greenfield and Carmichael [12e], that strong colloidal gold curves were more often associated with a high cell-count than a high total protein. In the 37 fluids in our series that had a protein content over 50 mg. only 15 (40 per cent.) had an abnormal gold curve, whereas 19 (79 per cent.) of the 24 fluids that had over 10 cells per c.mm. showed a zone I or mid-zone colloidal gold curve.

(5) *Other constituents*.—There is little in the literature with regard to the other characteristics of the cerebrospinal fluid in multiple sclerosis. Kafka [13] has studied the physical characteristics of the fluid (interferometry, spectroscopy, &c.). The only series of cases previously reported which has included a complete chemical examination of the fluid is that of Ayer and Foster [12a]. Their figures for the sugar, chlorides and non-protein nitrogen are in accord with our data. They examined the fluids also for creatinin content (4 cases, 1.2 to 2.38 mg. with average of 1.78 mg.), urea content (6 cases, to 0–24.3 mg., with an average of 15.5 mg.) and acetone (11 cases, none found).

Colloidal tests other than the colloidal gold have been studied [14]. The colloidal benzoin, mastic tests, &c., usually gave results less positive than the colloidal gold test.

(6) *Correlation between cerebrospinal fluid findings and the clinical course.*—Only few observers have made any effort to correlate the clinical course with the cerebrospinal fluid findings. They all agree that an entirely normal fluid may be found in acute or rapidly advancing cases, and a markedly abnormal fluid may be found in stationary cases. Our observations and those of Ayer and Foster [12a] would indicate that there is, however, a rough degree of correlation between the clinical course and the cerebrospinal fluid findings; the acute and progressive cases showing a much greater percentage of abnormalities than the stationary cases. Müller [12i] stated that the presence of a first zone (paretic) gold curve indicated that the course of the case would be one of remissions and exacerbations. Rogers [12l] felt that there was no definite relationship between the clinical course and the changes in the gold curve, and that there was no evidence that therapy produced any changes in the colloidal gold curve that might not occur spontaneously. Our results, as well as those of Ayer and Foster [12a], suggest that a pleocytosis greater than 10 cells per c.mm. indicates a progressive case. Our statistics also show that the combination of an abnormality in cells, protein and the colloidal gold test occurs only in progressive or early cases.

The occurrence of a positive Wassermann reaction in the cerebrospinal fluid is considered as excluding the diagnosis of multiple sclerosis.

SUMMARY.

(1) The cerebrospinal fluid findings in 100 cases of multiple sclerosis are reported and findings in 968 previously reported cases are summarized.

(2) The cerebrospinal fluid is absolutely normal in less than 20 per cent. of the cases of multiple sclerosis.

(3) The intracranial pressure is usually normal, but may occasionally be very slightly elevated. A pressure greater than 200 mm. of cerebrospinal fluid is practically never found.

(4) Pleocytosis of a moderate grade (6 to 40 cells per c.mm.) is a frequent finding. It occurred in 28 per cent. of the recorded cases.

(5) A quantitative abnormality of the protein content of the fluid was present in 45 per cent. of the reported cases. A quantitative increase in the protein content above the arbitrary normal limit was present only in 24 per cent.

(6) An abnormal colloidal gold curve was present in 71 per cent. of the cases. These abnormalities were divided as follows:—

First zone curve	..	..	25 per cent.
Mid-zone curve	..	..	22 „
Other abnormalities	..	..	24 „
Total	..	..	71 per cent.

(7) The fluid is usually normal in regard to its chloride, glucose, non-protein nitrogen, calcium, phosphorus, sodium, total solid content and freezing point. The cerebrospinal fluid Wassermann is always negative.

(8) There is a rough degree of correlation between the clinical course and the cerebrospinal fluid findings. A higher percentage of abnormalities is found in the fluids of active cases than in the fluids of stationary cases. A pleocytosis of over 10 cells per c.mm., or an abnormality in cells, protein and colloidal gold all in the same case are found only in progressive cases.

(9) There are no changes in the cerebrospinal fluid that are pathognomonic of multiple sclerosis. The presence of a first or mid-zone colloidal gold curve with or without a slight pleocytosis and increased protein content, in an otherwise normal fluid, is supporting evidence for the diagnosis of multiple sclerosis in a clinically suspicious case. This is only true if there is no history of syphilis or anti-luetic treatment.

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THE SYNDROME OF THE PREMOTOR CORTEX IN MAN : IMPAIRMENT OF SKILLED MOVEMENTS, FORCED GRASPING, SPASTICITY, AND VASOMOTOR DISTURB- ANCE.

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THE symptom of forced grasping has long been recognized in man, but the physiological basis of this phenomenon is not yet clearly understood; nor has it been sufficiently appreciated that forced grasping is invariably associated with a number of other equally striking clinical signs which together form a well-defined clinical entity. The case herein described illustrates the syndrome in all its features, and is perhaps of greater significance from the point of view of localization than many previously reported cases of forced grasping, since the lesion proved to be a removable tumour restricted to the premotor area of the cerebral cortex (area 6 of Brodmann).

I.—PREVIOUS OBSERVATIONS.

As early as 1903 Steinert [23] reported a case of tumour of the left "paracentral lobule" (the premotor area) in which "tonic innervation" of the right arm was present. Since that time there have been many reports of clinical cases showing the same phenomenon. The pathological reflex status of these cases has been variously termed "tonic innervation" (Steinert [23], Liepmann [16], Wilson and Walshe [26]), "palmar reflex" (Riddoch and Brain [19]), "Greifereflex" (Schuster and Pinéas [22]), and "forced grasping" (Adie and Critchley [1]).

Clinical studies.—Perusal of the extensive literature of this subject indicates that the clinical picture usually depicted in case histories is surprisingly definite, despite uncertainty concerning both the site of the lesion and the nature of the phenomenon itself, whether "voluntary," "involuntary," "associated" or purely "reflex" in character. In all clear-cut cases of unilateral reflex grasping the following symptoms are

associated with it on the affected side: increase of tendon reflexes, spasticity, hemiparesis or awkwardness of the extremities, and, occasionally, an extensor Babinski response. In addition nearly every case reported shows some psychic changes such as are usually associated with frontal lobe lesions: emotional instability, changes of character, or confusion and slowing of mental activity. There is scant reference, however, to vasomotor disturbance in the affected extremities.

In cases in which verification has been possible at autopsy, the *site* of the lesion has most often been the posterior part of the frontal lobe, just anterior to the motor or Betz cell area (Adie and Critchley [1]; Walshe and Robertson [25]); some authors, however, found that lesions of the corpus callosum may also be associated with the phenomenon, and still others have found lesions of the basal ganglia (Gullotta [11]) in cases of well-marked grasping.

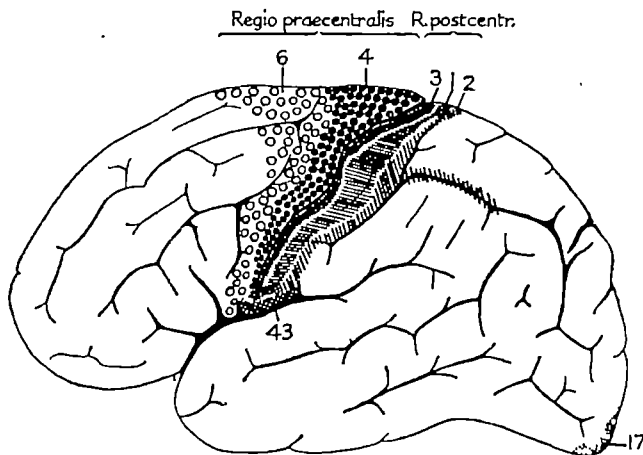


FIG. 1.—Left cerebral hemisphere in man, showing Area 6 (premotor area) and Area 4 (motor area). Reproduced from Brodmann's *Vergleichende Localisationslehre der Grosshirnrinde*.

Physiological studies.—In 1932 Richter and Hines [18] offered experimental evidence that a cortical lesion restricted to Brodmann's area 6 of the frontal lobe (fig. 1) produced involuntary grasping of the opposite extremity in rhesus monkeys. Later Fulton, Jacobsen and Kennard [9] by extirpation of the same area confirmed the findings of Richter and Hines concerning forced grasping, and in addition observed spasticity and increase in tendon reflexes on the side opposite to the lesion [15]. In these animals there was no evident alteration of behaviour. Further investigation of the problem by Bieber and

Fulton [2] demonstrated that the forced grasping resulting from a lesion of area 6 varies in intensity with the animal's position in space; they observed moreover that in monkeys from which the motor and premotor areas have been removed from both sides, the righting reflexes of Magnus and de Kleyn [17] are present, and they concluded that forced grasping is a part of the righting reflex mechanism peculiar to primates. It has also been found that lesions of area 6 cause temperature changes in the skin of the contralateral extremities (Fulton and Kennard [9], Kennard [14]).

II.—A CLINICAL CASE.

These experiments indicate that reflex grasping may be caused in monkeys by a cortical lesion restricted to the premotor area. That this is also true in man is clear from the following case in which a lesion affecting the homologous area of the cortex (without extending deeply subcortically) produced a syndrome practically identical with that seen in monkeys, forced grasping, spasticity and increased tendon reflexes being present in the contralateral upper extremity. In addition the phenomenon of grasping was influenced by change of position of the body in space, and the skin temperature of the affected side was abnormal.

Case 1.—Focal seizures, four years in duration, affecting left side of body, increasing rigidity, and awkwardness of left arm with forced grasping, increased reflexes and vasomotor disturbance; surgical removal of cystic glioma restricted to right premotor area; recovery with persistence of slight spasticity and grasping, and marked awkwardness.

Charles H. S. (Case No. 329817), aged 34, a white American shoe salesman, entered the Massachusetts General Hospital, June 9, 1933, complaining of "fits."

Present illness—focal seizures.—Four years before admission an epileptiform attack occurred, said to have been generalized in character, which began in his sleep and lasted for about fifteen minutes. In this first attack the left arm was more affected than the other extremities. During the following month he had three or four similar attacks at night, but the details of these attacks were unknown since they always commenced in his sleep. A few weeks later he had his first attack during the day. While engaged in painting a sign he noticed that his head and eyes turned involuntarily to the left, and that his left arm, though rigid, was "shaking" and drawn up against his body. He then lost consciousness and fell. Since that time he had had seventy-five or a hundred similar attacks of varying intensity, often three or four occurring in a single day. In the few months before admission they had been more

frequent, and during the previous eight months he had noticed that the left leg was also involved both in the "shaking" and the sustained contraction. Individual attacks always began in the index finger of the left hand, and spread subsequently to the other fingers and to the wrist, arm, side of the face, and sometimes to the left leg. If the attack was going to be a severe one, with loss of consciousness, his head and eyes turned to the left side just before he became unconscious. He had developed the habit of holding the arm close against the body and of grasping his left hand, especially the index finger, with the right in order "to prevent the attack from coming on."

Since the onset of his illness there had been increasing awkwardness and stiffness of the left arm, and it had come to be impossible to use it for delicate manipulations, though there was still a powerful grip. For six months he had been conscious of inability to release the grasp of his left hand, and he had ceased making any attempt to use it because such effort was likely to bring on a seizure.

When his spells began, four years previously, he had considerable bilateral headache at the time of the attacks. More recently the headache had become less severe, and at times he had been quite free from it.

Within eight weeks of admission the patient had noticed that the left hand had become redder and warmer than the right hand. At times the hand was "swollen," a condition which was not constant, but occurred at irregular intervals, lasted for an hour or two and disappeared completely.

There had been no nausea or vomiting, and no visual disturbance; and at no time had his left extremities been completely paralysed.

Past history.—His general health had always been good, and the only illnesses reported were measles and mumps in childhood. There had been a small hæmorrhage from the left ear six months before entrance; the cause was not ascertained, but there were no after-effects. In 1917 he had been hit in the forehead with a baseball, with a short period of unconsciousness. There were no known sequelæ.

Physical examination (June 9, 1933).—His general physical examination revealed a fairly well-nourished young male with no abnormalities of significance apart from moderate ichthyosis of extremities and chest, chronic infection of the tonsils, and carious teeth without apical abscesses. His blood-pressure was 124/92.

Neurological examination.—The patient proved highly intelligent and co-operative. His olfaction, vision, visual fields and optic discs were normal. Abnormal findings were confined to the *left* half of the body. There was slight weakness of the left side of his face, particularly the lower half, involving the muscles around the corners of the mouth. The left arm was weak, especially in the grip, but there was no paralysis or atrophy.

Reflexes.—These were slightly greater in the left arm and leg, and there was a definite left ankle clonus, but plantar stimulation gave strong flexion of the toes.

Sensation: There were no gross sensory changes to touch. Stereognostic sense and two-point discrimination were normal.

Forced grasping: Any pressure on the flexor surface of the fingers of the left hand, particularly if it was sufficient to stretch the flexor tendons slightly, caused strong involuntary grasping. It was not induced by merely stroking the skin of the palm. With the appropriate stimulus, however, there was a slow involuntary flexion of the fingers, sometimes clonic and sometimes sustained in character. Relaxation was slow and apparently involuntary. This reflex grasping was augmented when the patient lay on his right side (the side of the presumed brain lesion) and lessened with the patient on his left side, although it was feebly present in this position.

Vasomotor changes: The left hand was redder and warmer than the right, and showed no oedema. There were no obvious thermal differences between the two legs.

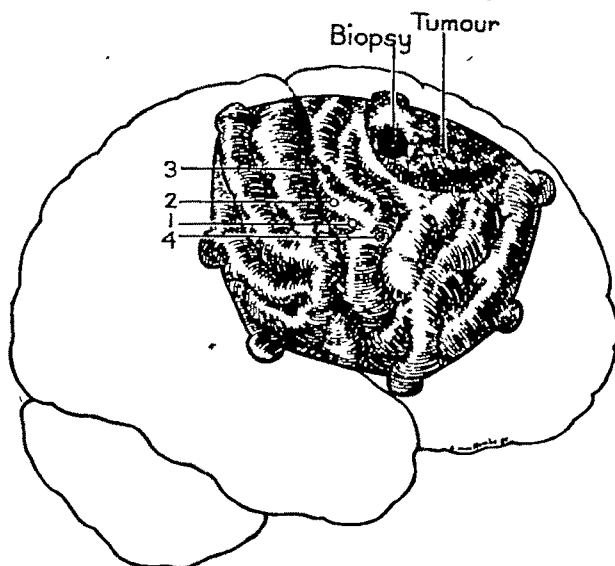


FIG. 2.—Reconstruction of the right cortex from callophane tracing made at the first operation, showing site of tumour mass. Stimulation of Point 1 produced movements of the left forefinger; of Point 2 produced elbow movement; of Point 3 produced a Jacksonian attack; of Point 4 produced twitching of the left face followed by a Jacksonian attack.

Roentgenographic examination of skull: The size and shape of the sella turcica was within normal limits. There was no evidence of increased intracranial pressure. The pineal gland was not visible. No unusual areas of calcification were seen. There was an ill-defined area of slightly diminished density in the frontal bone just to the left of the midline. Running to this were two rather large blood-vessel grooves.

Laboratory reports.—The urine was normal in eight examinations. Blood (June 9): W.B.C. 4,700; R.B.C. 4,800,000; Hb. 90 per cent.; differential count normal. Lumbar puncture (June 9): Clear, colourless fluid; initial pressure 155 mm. of water, combined jugular compression 450, right jugular 290, left

jugular 300; pressure after withdrawing 5 c.c. 140; after withdrawing 10 c.c. 110; cells 0 per c.mm.; total protein 30 mgm. per 100 c.c.; gold sol 0000000000; Wassermann test negative.

First operation, June 19, 1933 (Dr. W. Jason Mixter).—Under local (novocain) anaesthesia a tripod incision was made in the right side of the scalp and a large bone flap turned down. The fissure of Rolando and the surrounding brain were thoroughly exposed. The dura was reflected upward, above the leg area, almost to the midline. Rather high up in the precentral region, apparently just anterior to the precentral gyrus, was an abnormal area of cortex about 3 cm. across, in which the sulci were absent (fig. 2). There were several large veins at the periphery, but almost none in this abnormal area, which was slightly purplish in colour, in contrast to the surrounding brain. This abnormal area had the appearance of an infiltrating glioma. It was possible that the edges represented gliosis about the tumour rather than the tumour itself. There was no increase in intracranial tension, and the area described, although slightly elevated above the surrounding brain, was not abnormal to touch. A piece was removed for examination.

Stimulation of the cortex.—Monopolar faradic stimulation was carried out at four points, just posterior to the mass and apparently in the precentral gyrus (fig. 2). The strength of current used, the weakest available, was probably too strong for discrete localization. On stimulating point 1 in the motor arm area, anterior to the fissure of Rolando, movements of the left forefinger were noted. Stimulation of point 2 gave elbow movement; stimulation of point 3 produced a Jacksonian attack, which started in the forefinger and spread to the hand, arm, face and leg on the left side. This lasted about fifty seconds. After the attack a small subpial hæmorrhage was seen over the tumour. In about ten minutes the cortex was again stimulated at point 4, probably in the face area of the motor cortex. This produced an immediate twitching of the head and face, followed in about sixty seconds by twitching of the left hand and in about a minute and a half by twitching of the left leg. All four extremities then became involved, and the attack lasted about one minute longer.

The diagram (fig. 2) was reconstructed from a tracing of the sulci and blood-vessels made on cellophane at the time of the operation. The tumour was outlined with ink. The points stimulated were placed upon a reconstruction made from the cellophane tracing.

Pathological report (Dr. Charles S. Kubik).—*Biopsy*: A small fragment of soft red tissue, examined microscopically, showed tumour tissue with many bipolar cells and fibrous glia. The pathological diagnosis was glioma, probably astrocytoma (see below). The total protein of the cystic fluid was 5,460 mg. per 100 c.c.

Post-operative notes.—For a few days after operation the patient's left hand was completely flaccid, with disappearance of forced grasping. The Babinski response became positive. Power and forced grasping returned after a week, and there were no Jacksonian attacks. A second operation was performed three weeks after the first.

Second operation, July 7, 1933 (Dr. W. Jason Mixter).—The old incision was reopened and the tumour exposed as before. Bone was cut away at the upper edge of the flap to give wider exposure, and the dura reflected almost to the longitudinal sinus. The pial veins running from the region of the longitudinal sinus were clipped and cut. Mass silk sutures were placed in the brain around the tumour. The tumour was then dissected out, leaving a margin of fairly normal brain tissue, the dissection approaching very closely to the precentral gyrus, presumably in the arm area. On making this dissection, a good-sized cyst containing yellowish fluid was found beneath the tumour with a mural nodule of tumour tissue projecting into the cyst. No attempt was made to dissect the whole wall of the cyst; all tumour tissue was apparently removed.

Pathological report of tumour and cyst (Dr. Charles S. Kubik).—A mass of tissue of firm and somewhat rubber-like consistency, measuring 5·5 by 4 by 1 cm. and weighing 16 gm., was examined. One surface was reddish in colour and covered with a thin, transparent membrane, containing fair-sized blood-vessels and resembling pia-arachnoid. The other surface was opaque and white in colour, smooth and glistening; in one part of it there was a slight elevation, 1·5 cm. in diameter, consisting of hæmorrhagic, soft, necrotic tissue. Incisions in various parts of the specimen revealed a pale, homogeneous cut surface. The microscopical appearance was similar to that seen in the previous biopsy, that is, areas of dense fibrous glia and bipolar cells and other more cellular areas with very little fibrous glia. Some fairly well-formed astrocytes were noted. Pathological diagnosis: Astrocytoma.

Post-operative notes.—First day: The patient was sitting up in bed, talking freely, and had practically no post-operative symptoms. There was complete flaccid paralysis of the left arm, so that the grasp reflex could not be tested. He had had no Jacksonian attacks since the operation, a period of twenty-four hours.

Fifth day: The patient showed no abnormal mental symptoms and was very co-operative; he was a little emotional but otherwise normal. There was a well-marked left facial paralysis, central in type, and deviation of the tongue to the left. In the left arm there was no voluntary movement in the fingers, wrist, elbow or shoulder, and no sensory change to touch, but the sense of position in the fingers seemed slightly impaired. The abdominal reflexes were equal and active. There was some general weakness of the left leg, but all movements were possible. Sensation to touch appeared normal, but the sense of position of the big toe was impaired. The knee-jerks were equal, but difficult to obtain. Ankle clonus was easily obtained on the left. There were normal plantar responses on both sides.

Twelfth day: The patient had an attack of gross, jerky movements of the left side, beginning in the fingers of the left hand and extending up the arm to the side of the neck and into the face. The left side of the face was drawn up in the same gross movements. There was no loss of consciousness.

Thirteenth day: Flaccid paralysis of the left arm was still present and was most marked in the fingers and hand. The arm could be slightly flexed at the elbow voluntarily. Power in the left leg had become nearly normal.

Nineteenth day: The patient had another attack in the left arm, which again began with stiffness of the hand, followed by shaking in the shoulder, spasms of the side of the face, and some stiffness of the leg. There was no loss of consciousness and the patient considered it one of his lighter attacks. At this time power of the left arm was increasing daily and he could now raise the arm above his head. The fingers and wrist still showed complete paralysis.

Twenty-fifth day: The patient was discharged from the hospital. The decompressed area beneath the right temporal muscle was not distended. The left side of the face, around the corner of the mouth, showed a well-marked emotional type of paralysis, with some weakness on attempting to show the teeth. The left arm was somewhat stiffer than the right, with more active deep reflexes and a moderate degree of spasticity, but no loss of sensation. There was sometimes considerable trembling of the whole limb on attempted movement, not exactly of the intention tremor type, but a coarser, more rhythmic tremor. Power at the shoulder and elbow were almost normal. The wrist could be voluntarily extended to a point slightly beyond the midline. The fingers showed less power of extension, although all except the thumb were moved slightly. Voluntary flexion was better, although the hand could not be closed when the wrist was acutely flexed. Much of the power in the hand had reappeared in the preceding forty-eight hours. The left leg showed no paralysis, all movements being possible. There was slight weakness, however, at the ankle and the leg was somewhat stiffer than the right. The deep reflexes were increased and there was an easily elicited ankle clonus. The plantar reflex was plantar flexor. There was no loss of sensation in the leg.

Forced grasping: While lying on his back there was a moderately well-marked and easily elicited "grasping reflex" in the left hand when the palm was stroked from the wrist to the base of the fingers. Most of this reflex occurred in the fingers themselves, which were curled up in a position of 50-degree flexion and could not be relaxed. The reflex was more easily stimulated when the palm was stroked slowly. It did not appear to extend into the elbow or the shoulder. When the head was rotated sharply either to the right or to the left there was no change in this grasping reflex. However, when the patient turned his whole body to the right so that he was lying on his side, the reflex was increased very markedly in strength, so that the fingers were pulled away from the palm with considerable difficulty. When the patient turned on his left side, the reflex was somewhat diminished, but was practically the same as when he was lying on his back. The abdominal reflexes were present in all four quadrants, very easily elicited on the right side and fairly easily on the left.

The patient was cheerful and mentally active, taking a great interest in the examination. There were no signs of mental deterioration.

Twelve weeks (October 1, 1933): The patient was seen (by H. R. V.) at his home. He was up and dressed, walked, and seemed perfectly normal in his attitude and movements. He gave the following history of events since he

left the hospital: Early in August he had two slight attacks in his left arm, consisting of clonic movements, largely at the elbow, without movements of the fingers. There was no unconsciousness. Following this he was perfectly well for eight weeks, during which time he had been out nearly every day, and for a period of a day or two served as a shoe-store clerk. He had no difficulty in doing the work except that his left hand was a little awkward in tying up shoestrings. There was no stiffness of the fingers and no tendency towards spasm or shaking. His hand was a little clumsy in feeding himself and fastening his clothes, but he was able to carry out all the usual movements without any marked difficulty. On September 28 he had a severe attack.

Other symptoms during the preceding two months had been as follows: He had not had headache, but there had been some neuralgic pains across his forehead. His eyes got a little tired and occasionally he had blurred vision. For some weeks his left hand had felt a little stiff. This had now entirely disappeared except possibly in the middle finger. He thought the grasping which he noticed before the operation, which was then so marked that he had difficulty in letting go of his clothes in attempting to put them on, had disappeared. There had been some swelling of the hand, from time to time, but this was no longer noticeable. The hand usually felt hot, but never cold. At times he thought it a little redder than that of the right side.

Examination (October 1, 1933): The scar was nearly healed and the bones not elevated. There was possibly a little weakness of the left side of the face, particularly around the corner of the mouth, but this was not very evident and was only observed at times. The left arm was somewhat atrophied throughout, particularly in the shoulder and upper part. Voluntary power, however, was present in all muscle groups. There was no paralysis and all movements were easily performed. The posture of the muscles seemed essentially normal. Deep reflexes, however, at the elbow and wrist were increased on the left side and Hoffmann's sign was present. The knee-jerks were equal. There was no disturbance of gait. There was no loss of sense of touch.

Forced grasping: This was still present in the left hand, being particularly evident when the patient lay on his right side. Stroking the palm caused the fingers to be flexed so that they were straightened out with considerable difficulty. When the patient lay on his back, this reflex was still present, although much less, and when he lay on his left side there was no evidence of the reflex being present at all.

Thirteen weeks (October 7, 1933): The patient was seen in the Out-patient department of the Massachusetts General Hospital (by H.R.V. and J.F.F.). He reported no change in his condition since last seen, but the additional information was obtained that, prior to the appearance of motor disability in the left arm, the patient had noted that this extremity had seemed warmer and had sweated more. Since operation the left hand had been markedly warmer than the right and his left hand, arm, ear and face had been given to profuse sweating. For a time the left hand had been oedematous.

Examination revealed exaggerated reflexes in the left upper extremity, i.e., biceps, triceps and radial, and a Hoffmann's reflex was elicitable from the tip of each digit. The abdominal reflexes were weaker on the left than on the right, but the knee-jerks and ankle-jerks appeared equal. There was an exaggerated plantar flexion on the left.

Forced grasping was also observed; very gentle contact with the skin of the palm did not in itself evoke grasping with the body in any position, but contact with the palm or skin at the base of the digits, especially when the patient's attention was diverted, caused a fairly prompt, involuntary grasp, which became exaggerated as one pulled slightly on the flexor tendons. This response was definitely more exaggerated when the patient lay on his right side but became greatly diminished and sometimes could not be elicited when the patient was on his left. With a little effort, even when lying on the right side, the patient could relax his grasp, but there was sometimes a considerable interval between command and execution of the extensor movement. Motor performance was normal apart from evident awkwardness in using the left fingers, as in dressing and undressing. Large objects could be picked up effectively with his left hand, but small objects were much less successfully manipulated. There was no disturbance in gait. Vasomotor disturbance was obvious in the left hand and forearm, which were pinker than the right. There was no oedema. There was no difference in colour or temperature of the two lower extremities, but the left ear was much redder than the right. Moisture of the left hand was greater than that of the right. The eye-grounds and extra-ocular movements were normal. There was slight weakness of the left corner of the mouth. The patient continued to be unaware of reflex grasping in the left hand with ordinary motor performance.

Subsequent history.—The patient reported (November 14) that motor power was improving and that involuntary grasping had become much less troublesome since he was last seen. Seven months after his operation (February 10, 1934) his condition remained relatively unchanged. There had been two Jacksonian attacks in the last three months. Forced grasping was only feebly elicited.

III.—DISCUSSION.

The premotor syndrome, which this case and many others in the literature [1, 8, 11, 22, 25] so well illustrate, is characterized, when fully developed, by four distinctive symptoms which generally appear in definite chronological sequence: (i) inability to perform skilled movements, particularly with the digits, without gross impairment of motor power; (ii) spasticity with marked increase of deep reflexes, especially of the digits (sign of Hoffmann); (iii) forced grasping which may be influenced by the position of the body in space; (iv) vasomotor disturbances varying in degree from a slight alteration of temperature to states of marked oedema and hyperhydrosis.

The presence of Jacksonian seizures, spasticity, weakness and increase of reflexes, would not in themselves suffice to distinguish a motor from a premotor lesion of the cortex, for in cases of long-standing motor area lesions generalized weakness and Jacksonian seizures are also prominent symptoms, deep reflexes are likely to be increased, and spasticity may appear late. Foerster and Penfield [7] have pointed out, however, that the Jacksonian seizures produced by premotor lesions (Area 6a β) tend to be adverse in type, i.e. beginning by turning of the head as in this case, whereas sharply focal seizures beginning in a single muscle denote a lesion nearer the central sulcus, i.e., in Area 4 or the caudal part of Area 6a α .

Chronology of symptoms in premotor lesions.—Forced grasping, and probably also vasomotor disturbances, are likely to appear late in the history of cases with premotor lesions, and it should be possible by a careful study of the chronology of symptoms to establish a localizing diagnosis before forced grasping appears. Gradually increasing awkwardness in an extremity, affecting more particularly highly integrated digital movements, such as those involved in sewing, piano playing, buttoning a shirt, in itself suggests a premotor lesion, provided the awkwardness is not accompanied by tremor, resting or intentional. Jacksonian attacks may or may not occur, but spasticity and the increase in tendon reflexes develop early. The grip and other gross movements of the extremity do not become seriously impaired until the awkwardness, spasticity and forced grasping are fully developed.

Chronology of symptoms in motor area lesions.—In gradually expanding lesions of the motor area, on the other hand, generalized weakness of the extremity, especially of the grip, appears precociously, there is no forced grasping, and spasticity, if present at all, appears late. Acute injuries (as in the above case after the second operation), or rapidly expanding lesions of the motor area, produce flaccid paralysis and generalized depression of the reflexes.

We may now discuss the individual symptoms of the premotor syndrome in relation to the corresponding symptoms observed in monkeys and apes after premotor lesions [9, 14, 15].

Experimental destruction of the premotor area in a monkey or chimpanzee reproduces the premotor syndrome in its fully developed state, i.e. marked vasomotor disturbance, forced grasping, spasticity and failure of every type of skilled movement, and it is highly significant that during the period of recovery from such an experimental lesion the symptoms to disappear first (forced grasping and vasomotor

disturbance [14, 15]) are those which appear latest in the clinical premotor syndrome; while the symptoms which persist longest following the experimental lesions (impairment of skilled movements and increase of reflexes [14, 15]) are those which appear first in the clinical anamnesis. The precocious disturbance of skilled movements may therefore be regarded as the most significant feature of the premotor syndrome.

(1) *Impairment of skilled movements*.—Appearing first in clinical cases and persisting longest in experimental animals, the disturbance of acquired skilled movements may be looked upon as the primary symptom of lesions of the premotor area. This is not a new conception in clinical neurology, for the premotor region has, since the work of Campbell [4] in 1905, or possibly earlier, been looked upon as the part of the brain in which "motion formulæ for skilled acts are constructed and retained" (Tilney and Riley [24]); but the experimental analysis and proof of the correctness of this inference is new and deserves brief mention. In a series of monkeys and chimpanzees trained to perform complex manipulations ("problem boxes"), Jacobsen [12, 13] has shown that following removal of the premotor area, gross impairment of all forms of skilled movement still persists after forced grasping and spasticity have passed off as demonstrated by the animal's reluctance to use the affected extremity, and its awkwardness in carrying out any manipulations requiring delicate adjustment of movements.

(2) *Spasticity and increase of reflexes*.—When well developed, the spasticity of a premotor lesion closely resembles that occurring in hemiplegia. The associated increase of reflexes is seen most prominently in the deep reflexes of the digits, i.e. the signs of Rossolimo, Mendel-Bechterew and Hoffmann, and those signs may persist after unilateral lesions in animals, even when spasticity has become slight or scarcely demonstrable [15, 20]. When bilateral lesions of the premotor area have been made, the degree of the spasticity, and possibly also of the increase of reflexes, varies with the animal's position in space, the extensors being most spastic when the animal lies on the affected side.

Of the superficial reflexes only the plantars have been studied experimentally; the phenomenon of lateral deviation of the toes appears to be a premotor symptom [15], sometimes associated with exaggerated plantar flexion. The case just reported showed exaggerated plantar flexion after operation, but there was little fanning of the toes.

(3) *Forced grasping* [8A].—The reflex grasping exhibited by the above

case was typical of that previously described in other cases by Adie and Critchley [1], Freeman and Crosby [8], Davis and Currier [5], and others [11, 25], in that it was brought on by stimulation of the palm of the hand at the base of the fingers, or by putting the flexor tendons of the fingers very slightly on stretch (Walshe and Robertson [25]). Voluntary relaxation, moreover, was difficult. This particular case showed the striking phenomenon first observed in experimental animals [2], namely, a variation in the strength of the reflex with change of the patient's body in space. That is, the reflex was exaggerated when the patient lay on his right side with the affected extremity uppermost, and was diminished with the patient on his left side. This phenomenon has been observed experimentally after extirpation of the premotor area in monkeys [2], and was also seen by Magnus in 1922 [17] in thalamic monkeys. The increased force of flexion of the digits in the uppermost extremities is a part of the pattern of righting reflexes in thalamic preparations as it is in the monkeys with bilateral cortical extirpations of the premotor and motor areas. The same phenomenon, but less marked, appears for a short time after unilateral extirpation of the premotor area in monkeys, and it is of this type that the response must be in the present patient in whom the lesion is unilateral.

(4) *Vasomotor changes*.—The changes in the temperature of the skin on the left side in this patient are likewise of interest, as they would seem to indicate a cortical control of sweating and of the vasomotor system. It is a well-known clinical fact that patients with hemiparesis frequently show œdema and vasodilatation of the affected extremities, but this has usually been attributed to disuse. In this patient the temperature changes were present, without paresis, and affected face, ear and leg, as well as the left upper extremity. Gowers [10, vol. ii, p. 77], in 1888, was fully aware of the relation between the cortex and skin temperatures. Thus he describes vasomotor and "trophic" changes associated with cortical and capsular lesions in the following terms:—

"*Vasomotor and trophic changes*.—The paralysed limbs: (1) May present no vascular changes; (2) they may be warmer by half a degree or so than those of the opposite side; (3) they may be colder, pale or livid. Eulenberg and Landois have ascertained that the cortex contains, near the motor centres for the limbs, other centres that influence the vascular state of the limbs. Irritation of these centres causes pallor and coldness, while hyperæmia and increased warmth are probably the result of a loss of the central influence and may be due to disease of the cortex or of the path from it, which seems to pass in the posterior limb of the internal capsule. The elevation of temperature may be from 0.2° to 1.5° F. above that of the unparalysed side. It is often uniformly raised for ten

days or a fortnight, and then presents variations, sometimes an elevation, sometimes a depression. The elevation of temperature may be accompanied by redness of the skin; when the temperature falls the vessels may remain distended, and the limb then has a bluish-red aspect. Occasionally there is increased sweating. There may be some oedema of the subcutaneous tissue, most marked towards the extremity of the limb. This, in slight degree, is very common, and may come on at the end of one or two days and persist for many weeks."¹

In the subhuman primates there is always a change in skin temperature of the contralateral extremities following lesions of the premotor areas [14], but whether this is due to a change in the mechanism of sweating or to primary disturbance of vasomotor control has not yet been determined experimentally. Further analysis is also needed of the anatomical position of the vasomotor area.

IV.—CONCLUSIONS.

(1) A case of forced grasping is presented which, like other cases described in the clinical literature, exhibited spasticity, increase of the tendon reflexes of the digits, and gradual impairment of skilled movements of the fingers. These symptoms, together with vasomotor disturbances of the affected extremity, form a well-defined clinical entity which we have designated "the syndrome of the premotor cortex." All manifestations of the condition can be reproduced experimentally in the subhuman primates by lesions restricted to the premotor area.

(2) The premotor syndrome may be distinguished clinically from the motor-area syndrome on the basis of the chronology of symptoms. With premotor lesions, awkwardness, spasticity and increase of tendon reflexes appear early before the onset of motor weakness; whereas in lesions of the motor area weakness begins early, reflexes are at first depressed, and spasticity, if present, appears late.

(3) The forced grasping in the case herein described showed consistent variations with changes of position of the body in space, which places the phenomenon in the category of the righting reflexes described by Magnus [2, 8A].

(4) The changes in skin temperature and sweating on the side opposite the lesion indicates that representation of the autonomic nervous system exists in the cortex.

¹ The work of Eulenberg and Landois [6] demonstrated that stimulation of the region of the cruciate sulcus of dogs caused a change of temperature in contralateral extremities, whereas stimulation of the other areas of the cortex cause no such alteration.

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NOTICES OF RECENT PUBLICATIONS.

Anatomie du Système Nerveux. Par C. WINKLER. Haarlem: Erven F. Bohn. 1933. Pp. 367. 5me Partie.

It is fifteen years since the first volume of Professor Winkler's "Anatomy of the Nervous System" appeared, and those interested in this fundamental aspect of neurology have welcomed the succeeding parts which have been published in the interval. The present volume, which is devoted to the corpus striatum and the diencephalon, completes the system, for the author has unfortunately decided that the time is not yet ripe to describe fully the anatomy of the cerebral cortex and discuss its functional relationships.

The work has been a noteworthy achievement; it has undoubtedly a permanent value and will occupy an important and useful place among the many textbooks devoted to the anatomy of the nervous system. It bears the stamp of its author's individuality and is obviously based mainly on his own study and researches; in no sense is it a compilation. As the author is primarily a clinician it is natural that attention is directed mainly to those subjects that may have a practical application, in fact in its subtitle the volume is represented as an attempt to present as separate functional systems the tracts and centres by which sensory impressions are translated into reflex reactions.

In the first half of the book the anatomy and connections of the corpus striatum, which daily claim more attention owing to the increasing recognition of the rôle this part plays in the regulation of movement, are fully described. The author is uncertain whether the pallidum is devised from the telencephalon or diencephalon. On embryological grounds he recognizes a distinction between its occipital and frontal parts and believes that there is a functional distinction too, the latter being concerned in the dynamic mechanisms which effect co-ordinated movements, the former in the postural reactions of the trunk and limb girdles (the myostasis of Kleist). He accepts the existence of striopetal fibres from the cerebral cortex.

Owing to the complexity of the diencephalon, its separate parts, the epithalamus, the thalamus proper and the hypothalamus, are first described systematically in the simple brain of the rabbit and later in the human brain. From the physiological point of view the thalamus is regarded as an organ concerned in the simpler integration of sensations.

The printing of the volume and the reproduction of the numerous illustrations which it contains deserve the high praise of being worthy of the subject.

Weitere Beiträge zur Pathologie der traumatischen Gehirnblutungen.

Von O. BERNER. Oslo: Jacob Dybwad. 1933. S. 105.

Many years ago Duret drew attention to the frequency of small hæmorrhages around the aqueduct of Sylvius and in the floor of the fourth ventricle in the brains of persons dying from cerebral trauma, and attributed to these lesions an important rôle in the production of the symptoms of cerebral concussion. He regarded these small hæmorrhages as the result of an abrupt wave of cerebrospinal fluid impinging on the grey matter of the aqueduct and ventricle. Duret's observation and views received at the time of their publication considerable support from both pathologists and experimenters, but within recent years they have been largely neglected; in some recent monographs on cerebral trauma they are not even referred to.

Berner, of Oslo, has examined the brains of a large series of suitable cases and he has in almost all discovered the lesions described by Duret. In many cases these hæmorrhages are visible to the naked eye, but in others they can be demonstrated only in microscopical sections. In the fourth ventricle they lie chiefly near the middle line in front of the striæ acusticæ and in the anterior part of the mid-brain below the aqueduct. Larger hæmorrhages may be found in the grey matter of the pons. They are probably due to diapedesis rather than to rupture of vessels, and may be explained by Duret's hypothesis. Berner concludes that many of the symptoms of cerebral concussion are due to these circulatory disturbances in the medulla and pons.

This monograph is evidently based on a careful and methodical investigation, and cannot be neglected by anyone interested in the symptoms and pathogenesis of cerebral concussion.

La Syphilis du Cervelet et des Connexions cérébelleuses. Par J. THIERS.

Paris: G. Doin et Cie. 1934. Pp. 194. Price 20 fr.

Syphilis affects the cerebellum in much the same manner as it does other parts of the central nervous system, but as the lesions are generally due to occlusions of, or hæmorrhages from, vessels which supply the brain-stem too, the resulting symptoms are rarely referable to the cerebellum alone. Thiers has collected from recent French literature a number of observations, the causal lesions of which were of syphilitic origin, and attempts to group them into syndromes, many of which it must be said are artificial or unnecessary. The greater part of this monograph deals with "syphilitic cerebellar hemiplegia." In a few cases the lesions are purely cerebellar, but frequently the symptoms are due to affections of the cerebellar connections and they are then often associated with disturbances of cerebral, mesencephalic or pontine origin. Fuller descriptions of the lesions producing these syndromes would have been welcome. Gummata of the cerebellum and cerebellar lesions occurring in the course of the syphilitic disease of the nervous system are also considered.

Pink Disease (Infantile Acrodymia). By CH. ROCAZ. Translated by I. J. WOOD, M.D. London: Martin Hopkinson, Ltd, 1933. Pp. 153. Price 7s. 6d.

This small monograph brings the subject up to 1931, the date of the French edition. It gives a very full account of the symptoms and of what is known of the pathology of the condition, which the author considers to be produced by a primary disturbance of the neuro-vegetative system. He is inclined to accept Kuiper's view that the primary lesion is in the diencephalic nuclei; indeed he regards it as a form of encephalitis affecting this region of the brain. In favour of this theory he cites the initial pyrexia and the early lymphocytosis in the cerebrospinal fluid. The disease resembles encephalitis lethargica in the nocturnal insomnia with drowsiness by day, the myoclonus and the changes in temperament.

The English translation in some places follows the French idiom rather too closely, but it is for the most part clear. There is a full bibliography, but no index.

Human Mentality. An Outline of General Psychiatry. By BROR GADELIUS. Copenhagen: Levin and Muskgard. London: Humphrey Milford. 1933. Pp. 620. Price 30s.

Dr. Gadelius had until recently been for many years the Professor of Psychiatry in Stockholm, and this work was originally written to supply the lack of a Swedish textbook on the subject. The present volume is only half of the complete work; the remaining section deals with special psychiatry and no English translation of it has yet been published. It would be very welcome.

This book, written in clear and agreeable English, is informed by a psychological and psychotherapeutic interest. The author emphasizes how closely akin are the normal and the morbid phenomena in this field, and one has as a result a valuable presentation of psychopathology, erring neither on the academic nor the analytical side. Such an empirical psychology, as conceived by an experienced psychiatrist, is nearer to the facts with which the physician must deal than are the schemes of laboratory psychologists or of Freudians. To the latter Dr. Gadelius devotes a temperate but critical chapter, in large measure adverse.

The bulkiness of the volume is due to the author's intentional avoidance of a concise mode of presentation, for reasons which seem hardly valid in a textbook. It is, however, very easy to read, learned but not abstruse, and interesting; wide acquaintance with recent research is associated with sound judgment and excellent case-material. It would be impossible to name any other work which so happily demonstrates to the average reader that a true psychiatric psychopathology is being built up which is close to its material and

as fruitful therapeutically as in other ways, though restrained in its hypotheses and its application.

There are three sections, preceded by a historical and an epistemological survey. The first section deals with normal and morbid psychology or "functional structure of mental life," the second with the genetic and other causes of mental disease, and the third with treatment. The mode of approach throughout the book is individual but sound.

Sémiologie du Sommeil. Par A. TOURNAY. Pp. 131. Paris: G. Doin et Cie. 1934. Price 30 fr.

The interest in the nature of sleep which has been excited by recent physiological and pathological observations has led to the appearance of many monographs, but few of them are more comprehensive than, and yet so concise as, this book by Dr. Tournay. In the first two sections he describes carefully and analyses the bodily phenomena associated with sleep, as the state of the motor system, sensation, the special senses and the reflexes, as well as the visceral and metabolic activities. The second half of the book is concerned with the reciprocal influence of the cortex and subcortical parts of the nervous system in determining sleep and waking, and in a discussion of the probable nature of their activities in relation to sleep. The author brings no new facts to this discussion, but his clear and impartial summary of pathological and experimental observations will be of service to those unable to study the original publications and to all interested in this important biological problem.

Recent Advances in Psychiatry. By HENRY DEVINE. Second Edition. London: Churchill. 1933. Price 12s. 6d.

The second edition of this compendium of recent work has been enlarged to include chapters on heredity in mental disorder and on deficient oxidation, as well as a short one describing the mental concomitants of pernicious anæmia. The book bears everywhere the impress of Dr. Devine's wide acquaintance with the literature of the subject and of his tolerant and receptive attitude towards tendencies and schools commonly thought to be violently opposed or even fundamentally irreconcilable. This has led to the retention of some material now generally thought to be unsound, but the impartiality of the presentation is very evident. There can be no doubt of the value of such a work for English readers.

Nouveau Traité de Psychologie. Par GEORGES DUMAS. Tome troisième. Les Associations sensitivo-motives. Pp. 462. Paris: Alcan. 1933. Price 100 fr.

The third volume of this very useful system of psychology is like its predecessors in its succinct, though detailed, mode of critical presentation and in its attention to work done in other countries besides France, though often

the most recent foreign work is overlooked. The present volume is the work of two contributors, Professor Georges Dumas and André Ombrédane. It deals with the higher sensori-motor integration. Ombrédane gives a clear and penetrating review of the experimental data and conclusions regarding equilibrium and orientation. The following two sections, by Dumas, occupy the greater part of the book. The first is concerned with the expression of emotion and the second with expressive mimicry. Professor Dumas has been active in this field since the beginning of the century, and his recent studies on congenitally blind persons are of particular interest. His survey of the subject here is a notable contribution to a difficult and unduly neglected branch of psychology. The concluding section of the volume, on language, is by Ombrédane. It is brief, but this is a rare and welcome feature in writing on this subject. The writer is closely attached to the teachings by Charles Foix which aim at a cerebral localization of speech in two planes, as it were. He presents summarily the conflicting views on the pathological aspects of language but scarcely does justice to the work of the German school, represented by Goldstein, nor is there in this section a satisfying discussion of the problem of inner speech and its relation to thinking. On the whole this volume admirably fulfils its purpose.

Writers of "Original Articles and Clinical Cases" are supplied free of charge with 50 copies reprinted in the form in which the paper stands in the pages of "Brain." If reprints are required in pamphlet form, with wrapper, title-page, &c., and re-numbered pages, they must be ordered, at the expense of the writers, from Messrs. BALE, SONS & DANIELSSON, Ltd., 83-91, Great Titchfield Street, London, W.

Members of the Neurological Section of the Royal Society of Medicine can obtain the Index of "Brain" for the Volumes I to XXIII inclusive, that is, from its commencement to the end of 1900, from Messrs. MACMILLAN & CO., Ltd., St. Martin's Street, London, W.C., at the price of 8s. 6d., post free.

To those who are not members of the Neurological Section of the Royal Society of Medicine the price is 8s. 6d. net, and the volume may be obtained through any bookseller.

EDITOR.

JUNE, 1934.

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FAMILIAL PERIODIC PARALYSIS AND ITS TRANSITION INTO SPINAL MUSCULAR ATROPHY.

BY A. BIEMOND AND A. POŁAK DANIELS.

(*From the Neurological Service of Prof. Dr. B. Brouwer, Wilhelmina-Gasthuis, Amsterdam.*)

FAMILIAL periodic paralysis is a rare disease of a heredo-familial nature which manifests itself in a characteristic symptom complex.

Our knowledge of this disease dates back to the second half of the nineteenth century, when Cavaré (1853) described one case. Since that time many cases have been described. As most of the publications include a more or less complete résumé of the literature we will only mention the most important ones. For a complete summary of the literature the reader is referred to the monographs of Schmidt (1919) and of Janota and Weber (1928).

The symptom complex of familial periodic paralysis is essentially as follows: The patient is suddenly seized with a flaccid paralysis of one or more muscle groups, usually in more than one extremity. The tendon reflexes are entirely absent or depressed, and the electrical excitability of the affected muscles is diminished or absent to both the faradic and galvanic current. The trunk muscles are seldom involved, and only occasionally the muscles innervated by the cranial nerves. Sensation remains intact, although occasionally at the beginning of an attack paræsthesiæ may be present in the extremities.

The majority of attacks occur after inactivity; the patient may awaken to find himself paralysed. Sometimes the paralysis has been attributed to severe muscular exertion on the preceding day. Cold, various emotional states, and foods rich in carbohydrates have been mentioned as precipitating factors.

The duration and intensity of the attacks are variable; the seizures

may last from one hour to several days. There is no disturbance in the psychic sphere, although the patient is usually very irritable during the stage of paralysis. The function of the internal organs is not usually disturbed, although sometimes sympathetic disorder is manifested by irregularity of the pulse, dyspnoea, sweating and dysuria.

This short synopsis of symptoms suffices to establish this affliction as a disease *sui generis*. Hartwig (quoted by Goldflam) described in 1874 a patient, aged 23, in whom some attacks were associated with disturbances of speech, respiration and swallowing; he attributed these disturbances to a so-called "seröse Imbibition" of the brain-stem. In 1885 Westphal reported a case in which Oppenheim found that the excitability of the muscles was diminished quantitatively, that is relatively to the intensity of the paralysis. A reaction of degeneration was not found. During the attack Oppenheim heard a soft systolic murmur at the heart. Together with Siemerling he examined a small piece of muscle microscopically. We will refer to this again. Westphal was of the opinion that the attack was precipitated by a disturbance of the peripheral vessels resulting in a sudden disturbance of nutrition to the muscles. Oppenheim believed that an unknown virus was the causative factor.

Many authors have attributed the condition to auto-intoxication. The first to express this opinion was Goldflam who after an intensive study of a family in which there were eleven cases of familial periodic paralysis concluded that this disease must be considered as a primary myopathy resulting from some intestinal toxin. By chemical analysis of the urine and fæces and by histological examination of muscle, he tried to gather confirmatory evidence for his hypothesis. He claimed that the electrical reactions resembled those found in Thomsen's disease and in the newborn (Westphal). From this evidence he deduced the conclusion that in these cases of familial periodic paralysis the muscular system remained in the infantile state of development. Subsequent investigators were not able to confirm these findings. In 1886 Couzot recognized the familial nature of this disease. Crafts also was of the opinion that the disease was caused by auto-intoxication and tried to isolate a toxin from the fæces. Singer and Goodbody also favoured the toxic theory and claimed that the toxin affected the muscle fibres of predisposed individuals.

Janota and Weber expressed this same opinion in a recent monograph. These authors base their work on the well-known interpretation of the "Vegetative System" of Kraus and Zondek, according to which

the function of a tissue-cell depends upon the relation between the electrolytes and colloids in and around this cell. These, together with the nerve-endings in the cell, form a functional unit. A change in the equilibrium of the electrolyte-colloid balance gives an action current and thereby stimulates the nerve. In the same way stimulation of the nerve elicits a change in the cell system. According to Janota and Weber the presence of a toxin produces a change in the electrolyte content and consequently a disturbance in the excitability of the muscle.

Various arguments have been offered in favour of a disturbance of the autonomic nervous system. The fact that the attacks occur during the night when the vagus is active (R. Schmidt: "*In der Nacht wacht der Vagus auf*"), the changes in the electrocardiogram, the shifting in the blood of the potassium, calcium and magnesium, and the change in the blood-sugar and sweating suggest an autonomic imbalance. The conclusion that the disturbance is entirely due to vagotonia is not clear.

Most investigators believe that it is a question of some toxic process but differ on the point of action of the toxin. Putnam mentions a relation between familial periodic paralysis and epilepsy in that the toxin causes a preponderance of the inhibitory over the excitatory function. Buzzard thinks that as a result of the intoxication the metabolic products of muscle activity cannot be carried away through the lymphatics and so the muscular function is impaired. Holtzapple emphasizes a vasomotor disturbance of the anterior spinal artery. He draws an analogy with migraine which also may be found in families subject to periodic paralysis. As a result of the vasospasm a degeneration of the anterior horn cells with a subsequent muscular dystrophia may develop. In his publication the genealogy of a family was described in which there were several cases of periodic paralysis and muscular dystrophy. Oppenheim and Bernhardt had previously called attention to the connection of both these diseases. Bernhardt reported attacks of periodic paralysis in a father and a son who were both afflicted with progressive muscular dystrophy. Donath described a case of periodic paralysis which developed after trauma; he favoured the toxic theory. He investigated the effect of curare on muscle in experimental animals, but found no resemblance to the hypothetical toxin in periodic paralysis.

In Schmidt's monograph autopsies were reported in two brothers who died during attacks, but no abnormal findings were noted. He believes that in predisposed individuals a vasospastic ischæmia of the muscles is produced by an increase of adrenalin in the blood. He

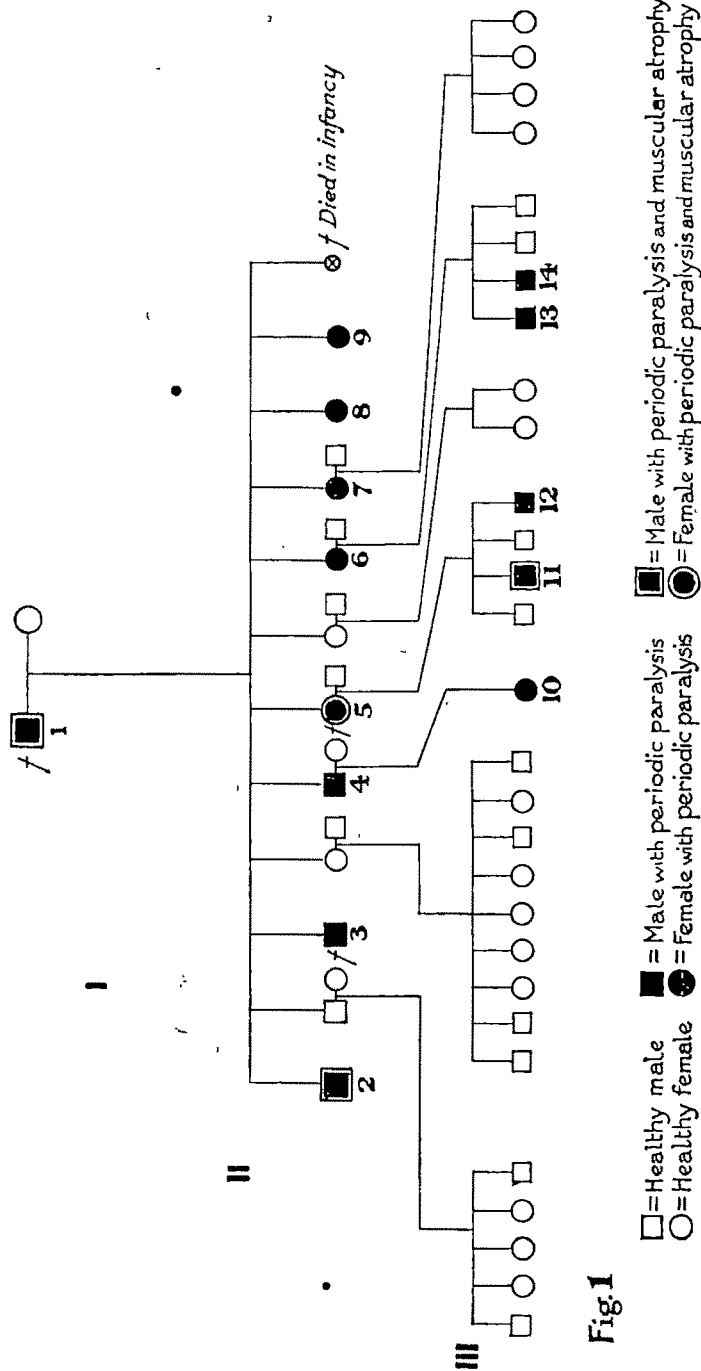


Fig. 1.

supposes that the increase of adrenalin is the result of an auto-intoxication. This is in contradiction to the postulate of Janota and Weber who described a vagotonic state. Maclachlan, who gathered two hundred cases from the literature, also emphasized the frequent association with migraine and toxic factors.

One isolated case of periodic paralysis has been reported in the Netherlands by M. de Bruin. There were no other cases in the family. The following is the description of the first Dutch family in which the periodic paralysis appeared in three generations in an unmistakable heredo-familial manner. In this non-semitic family fourteen cases appeared; twelve patients have been examined thoroughly and two of



FIG. 2.

the members are dead. Two patients were observed, one of them repeatedly, in attacks. The history of the latter will be reported in detail after a brief summary of the main points in the other thirteen cases. Fig. 1 represents the genealogical distribution in the family tree; the patients suffering with periodic paralysis are numbered from 1 to 14 (see also fig. 2).

Case 1.—The progenitor died in 1919 or 1920 in his 65th year, probably of carcinoma of the stomach. In his case the periodic attacks of paralysis began at the age of 18, but no further details are known. It is certain that in the last ten years of his life he was permanently paralysed in all four extremities, especially in the upper parts of the arms and legs, so that in the last five years of his life it was necessary to wheel him about in a chair. His wife never had any neurological disease, is still living and presents no particular symptoms.

Case 2.—The eldest son of Case 1 is now aged 54, and a complete examination was done by us several times. In his 8th year he began to have attacks which appeared during sleep. He awoke with paralysis of all four extremities. After about twelve hours power gradually returned. As far as he can remember there appeared no concomitant sweating or gastric symptoms. Nothing in particular could be recalled about the urinary excretion during or at the end of an attack. At the inception of the illness the attacks occurred with a frequency of about five or six a year, but after an attack of pneumonia with pleuritis in his 21st year, they became more frequent and of longer duration. In 1906 or 1907 he was for three months in a university clinic, but unfortunately the records cannot be obtained. At this time he complained of severe pains in his arms and legs. The treatment received in the hospital was of no avail and the attacks continued at irregular intervals until 1917 when they suddenly stopped.

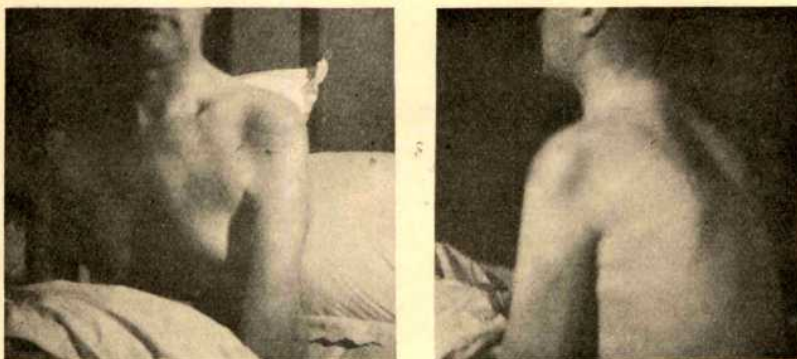


FIG. 3.

Soon after the cessation of the seizures a gradually increasing weakness was noted in the upper portions of the arms and legs. His gait became unsteady, it was difficult for him to rise from the sitting position and he observed a slowly increasing atrophy of the upper parts of the lower extremities. In 1921 he was examined in the neurological clinic of the University of Utrecht. Here it was observed that the thigh muscles were slightly atrophied and that there was a distinct ataxia and hypotonia of the lower extremities. In addition the ankle-jerks were absent and the knee-jerks were depressed. The diagnosis of tabes dorsalis was entertained in spite of the facts that the pupils reacted normally to light, there was no disturbance of sensibility or bladder, no Romberg's sign, and negative reactions of Wassermann and Sachs-Georgi in the blood. Since 1921 the weakness became more intense, so that since 1928 he was completely bedridden.

In 1933 there was a distinct generalized atrophy of the muscles of the shoulder-girdle and upper arms (fig. 3), with typical winged scapulae on both sides. The upper arms could not be elevated. The triceps did not contract; the biceps were very feeble. The forearms and the intrinsic muscles of the

hands functioned well. No fibrillary contractions were seen. The biceps and triceps reflexes were present and sensibility was intact.

The musculature of the trunk was weak and the patient was unable to rise to the sitting position in bed and to turn over on to his side. The abdominal and cremasteric reflexes were depressed bilaterally. There were no abnormalities of the vertebral column. Sensibility of the trunk was intact and the sphincters functioned normally. There was a marked atrophy of the thighs, but no distinct atrophy of the peripheral parts of the lower extremities. The muscles of the legs (especially the calf-muscles) felt somewhat soggy although there was no definite oedema. There was no suggestion of pseudohypertrophy however. No fibrillary contractions were seen. Whereas the movements at the hip- and knee-joints are impossible, dorsal flexion of the foot and extension of the toes were just possible on the right side, but absent on the left. Plantar flexion of the feet was performed with fair power. The muscles of the buttocks were atrophic. Sensibility was intact.

Electrical examination.—The extensor muscles of the lower legs (musculi tibialis anticus, extensor digitorum communis, extensor hallucis, peronei) show a typical slow contraction with the galvanic current, a distinct peripheral dislocation of the points of excitability and a reversal of the polar formula. With the faradic current only the peroneal muscles reacted. The thigh and calf muscles did not contract at all either to galvanic or faradic stimulation. In the arms the posterior portions of the deltoids gave a slow reaction while the anterior portions contracted quickly. The pectoralis major on each side also reacted slowly. In addition, the proximal parts of the upper extremities showed a generalized diminution in electrical excitability, while the forearms and intrinsic muscles of the hands reacted normally.

Finally it should be noted that there was an old suppurating fistula just above the left clavicle. It can be accepted that he has *tuberculosis* in addition to his muscular disease, especially since there was a history of pleurisy in the eleventh year.

Summary.—Patient 2 suffered with periodic attacks of paralysis in his arms and legs from the age of 8 years until his 38th year. After these attacks disappeared a gradually increasing weakness and atrophy of the thighs, and later also of the proximal portions of the arms, developed, so that in his 49th year he was completely invalided. At the age of 54 there was a diffuse atrophy of the muscles of the hips, shoulder-girdles and the upper parts of the arms and thighs, less atrophy in the legs and none at all in the forearms. In most of the affected muscular groups there was a definite reaction of degeneration. In addition the patient was suffering with an inactive type of tuberculosis.

Case 3.—This patient died in 1910, at the age of 20, in a hospital in Germany. The cause of death was reported as pneumonia. It is certain that

he began to have attacks when he was about 8 years old just as his brothers and sisters. His attacks were also similar in that they were nocturnal, never lasted more than twenty-four hours, involved both arms and legs and occurred at irregular intervals until his death. Further particulars are not known.

Case 4.—This patient is now aged 49 and his attacks also appeared about his 7th or 8th year and always came during the night. During his adolescence the attacks were frequent, but they decreased slightly in number but not in intensity with age. The seizures occurred at irregular intervals and the duration of the paralysis was variable. In severe attacks movements of the head as well as of the arms and legs were impossible. While he was afflicted he drank only water and refused to take any food because he had the feeling that it would have a bad influence on the attack. The recovery of motility was preceded by profuse perspiration and increased excretion of urine. During the attack the legs felt cold and the patient was certain that massage relieved him. He was unable to suggest any precipitating factor. He drank alcohol very sparingly. There was no history of migraine or tuberculosis, and apart from the disease of the muscular system his physical condition was good. There were no neurological abnormalities. The muscles are well developed and of normal volume. There are no myasthenic or myotonic phenomena, and all reflexes are present and active.

Case 5.—This patient was a woman who died at the age of 40 (in 1929) and the history was obtained from the family. In her case, too, the attacks started between the 7th and 8th year. At first they were not very frequent or severe, but in the course of time, however, they became worse. When she was a young woman the attacks occurred once in fourteen days during the spring and autumn months. Again, the attacks occurred at night and lasted one or two days at the most. Usually the arms and legs as well as the head and trunk muscles were paralysed. Occasionally as she was recovering from one attack she relapsed into another. This patient also took no food during the time she was paralysed, but drank water freely, especially towards the end of the attack when she began to perspire and urinate profusely.

In the last five years of her life she had some permanent paresis. She developed a steppage gait, raised herself from a sitting position with difficulty, was unable to run and in the horizontal position she was unable to raise her legs. She had more and more difficulties with her household duties. At this time her physician noted an atrophy of the shoulder and hip muscles. The tendon reflexes were markedly depressed. About the same time that the permanent muscular weakness occurred, there also appeared psychic change, particularly in the form of self-accusation. In 1927 she was in hospital for six months on account of the psychic disturbance. In 1928 there was a remission of the mental symptoms, and the depression returned again in 1929 and eventuated in suicide. No record of her stay in the hospital was obtainable.

Summary.—Patient 5 suffered from attacks of periodic paralysis

between the ages of 8 and 35 years. Then there developed a permanent weakness of the muscles of the shoulders and hips. About the same time there appeared psychic disturbances in the form of a depression, which ended in suicide at the age of 40.

Case 6.—This patient, a woman, aged 44, only had one attack of definite paralysis involving arms and legs, which occurred four years ago. This seizure was preceded by pain in the lumbar region and lasted two days. It is probable that she had abortive attacks previously, during which she had a sensation of weakness and coldness in the lower extremities. Application of heat resulted in return of function. During the last four years she was entirely free of symptoms. This patient suffered with repeated migrainous attacks, but these were not related to the attacks of weakness. No neurological abnormality was noted on examination.

Case 7.—This patient had her first attack at the age of 7 or 8 years. She became very feeble during the seizures, but was never totally paralysed. The paresis came on during the night and disappeared slowly in the course of the following day. The weakness was not as severe in the arms as in the legs, and was always symmetrical. She cannot recall any details about perspiration, thirst or antipathy to food during the attack. During puberty and pregnancy the attacks were more frequent and intense. In the last three years she was free from attacks. The patient also suffers from typical migraine. There were no neurological abnormalities. Her four children are all under the age of 8 years.

Case 8.—The patient is a young woman, aged 37, who began to have typical attacks of periodic paralysis at the age of 7 or 8 years, which have been recurring at irregular intervals until the present. In this case also the paralysis appeared during the night: she awakens to find herself completely paralysed and continues to be so for one day. During this time she abstains from food and drinks much water, especially towards the end of the attack. Recovery is preceded by profuse perspiration and polyuria. During puberty the attacks were very frequent and severe, but later they became gradually less frequent and less severe. This patient suffers with migraine and has occasionally had typical generalized epileptic seizures. She was rather backward in school and still gives the impression of being mentally retarded. On examination, no abnormal neurological findings were noted. In the last few years the attacks have occurred on rare occasions only.

Case 9.—In this case also the attacks began at the age of 7 or 8 years, lasted one or two days, and appeared with a frequency of four or five per year. The musculature of the head, trunk and limbs became totally paralysed during an attack. Speech, swallowing and the ocular movements remained normal. She was not able to recall any abnormalities of perspiration or thirst. Since the onset of puberty the attacks have gradually become less frequent and less intense. After her 21st year the attacks disappeared entirely. In this case there is also a history of migraine. Neurological findings were absent.

Case 10.—This patient is a young girl, aged 20, who suffered between her 13th and 17th year with transient attacks of weakness in her legs. Since that time she has been entirely free from attacks and the neurological examination revealed no disease.

Case 11.—This boy, aged 11 years, was under observation in the neurological clinic from March 9, 1933, until April 5, 1933. In his case typical attacks of paralysis of arms and legs first appeared when he was 6 years old. Prior to admission he had only had five attacks, the shortest lasting three to four hours, and the longest thirty-six hours. In one of these attacks both legs, but only one arm, were involved. Also in this instance the paralysis always appeared during the night. There were also typical concomitant vegetative



FIG. 4.

symptoms which were similar to those in Case 12, described below. Of further importance is the fact that in the summer of 1932 he was in hospital because of a protracted cough; tuberculosis was suspected, but not verified. The father noted more recently that the boy's legs, especially his thighs, had become weaker, and that his gait was not entirely normal. No attacks appeared while he was under our observation. The patient has marked winging of the scapulæ, although the elevation of the arms is fairly good (fig. 4). The Achilles reflexes are absent and the knee-jerks are depressed. We are convinced that there is a beginning muscular atrophy.

There are no definite disturbances in the electrical excitability of the muscles. The serological reactions were negative in the blood and spinal fluid. The Pirquet test was markedly positive, and the X-ray of the chest showed a widening of the hilar shadows and an increased density in the upper lobes

The blood examination showed a lymphocytosis (38.5 per cent.). It is probable, therefore, that the patient is suffering from an incipient tuberculosis. Further confirmation is afforded by the fact that he ran a subfebrile temperature while under observation.

Case 13.—This patient gave a history of several typical attacks of paralysis between the ages of 14 and 18 years, each of which lasted about twelve hours and involved mainly the legs, although the arms were not entirely free. The attacks occurred during the night and were preceded by a tired feeling in his back on the previous evening. He was thirsty during the attack, while profuse perspiration and polyuria announced recovery. The patient had the impression that the use of alcoholic beverages, especially beer, precipitated the paralysis. No abnormal neurological findings were noted.

Case 14.—This patient, a boy aged 19, had a few nocturnal attacks of paralysis of his arms and legs since the age of 14. The most severe attack lasted thirty-six hours. He had no appetite during the attacks. There were no associated autonomic symptoms. Occasionally he had abortive attacks, during which the legs were only feeble. No positive neurological signs were elicited.

Case 12.—P. R., aged 7 years. First admission from March 9 until April 4, 1933. The history obtained from the father was that the patient suffered with attacks of paralysis since the age of 4. The attacks appeared without any apparent warning or cause, and always during the night. The shortest interval between the attacks was several months, the longest was eight months. His last attack was six weeks prior to admission. The shortest duration was three hours, and the longest lasted for three days. There were seizures in which he was totally paralysed, and others in which the paralysis was partial. A complete description of an attack is as follows, and is characteristic of the attacks in all members of this family who suffered from periodic paralysis: Nothing unusual is noted on the day preceding the attack, but on awakening the patient finds that he is paralysed. He complains of numbness in the affected extremities, but there is no pain or sensation of pins and needles. Tactile sensation is unimpaired. During the attack he is nervous and depressed and tends to perspire more than usual. The extremities are of normal colour. He never complains of twitching, headache, dizziness, tinnitus or nausea. The appetite is decreased. Thirst is extreme, but the urine output is small, and constipation is common. This patient was backward in school. With the exception of measles, his past history was negative.

Examination.—The patient appears in good physical condition. No disease was found in the internal organs. The X-ray of the chest shows some calcification at the hilus. The examination of the blood and urine were negative. The blood-pressure was 118/85. There were no abnormal neurological findings. The electrical excitability and the strength of the muscles and their chronaxia were normal. The X-rays of the skull and the fundi were negative. The spinal fluid and the Queckenstedt test were normal. The electrocardiogram showed a slight preponderance of the right ventricle. The Wassermann,

gold-sol and Sachs-Georgi reactions in the spinal fluid and the serological reactions in the blood were normal. The water-balance and chloride output were unaffected.

Second admission, April 29 until July 8, 1933. He was brought in on the morning of June 29, suffering from a mild attack, which appeared during the preceding night. He was able to walk into the clinic, but was somewhat unsteady, and his gait was on a broad base. For the first time a fairly clear systolic murmur was heard over all his heart. The electrical excitability of all the muscles of the lower extremities was diminished. There was a trace of albumin in the urine and also very slight reduction with Fehling's solution.

The urea content of the urine was 30 gr. per litre. Again the spinal fluid showed no abnormality. The sedimentation rate of the erythrocytes and the leucocyte count were normal. After a few days there occurred an eosinophilia which remained for a week. No further leucocyte count could be made as the patient was discharged from the clinic. No ova or parasites were to be found in the faeces.

Third admission from December 29, 1933, until February 5, 1934.

After his discharge he remained free of attacks for several months, but recently the attacks returned, at first once or twice a week, and during the last ten days every night. They lasted a few hours, at the most twelve hours. During this period in the hospital an attempt was made to precipitate an attack by a diet rich in carbohydrates, restriction of fluid and forced muscular exertion, and a few times small doses of alcohol were given. Although he had four attacks they did not seem related to these measures. The attacks began about 10 p.m. and lasted only a few hours; the patient awakened, cried and was very irritable. During the attacks which we observed the muscles of the hips and shoulder-girdle were most severely paralysed. In the standing position he had to be supported as if he were suffering from muscular atrophy. The tendon-reflexes were usually hyper-active at the beginning of the attack and depressed later. They were similar on both sides. The superficial reflexes were normal.

During the first attack the electrical excitability of the muscles was diminished. A small piece of muscle was excised and examined histologically.¹ During the third attack a lumbar puncture was done again. The spinal fluid, including the gold-sol curve, was normal. A chemical analysis of the blood was made and these values were compared with a similar examination that was made a few days later during an interval (fasting-period).

A. Blood taken during the attack at 23.15 p.m. and analysed on the following morning at 10 a.m.

B. Blood taken during an interval and analysed immediately.

	Calcium	Potassium	Magnesium	Phosphorus	Lactic acid
A.	11.15 mgm. %	18.38 mgm. %	4.45 mgm. %	4.44 mgm. %	26.33 mgm. %
B.	10.69 mgm. %	17.87 mgm. %	3.49 mgm. %	5.88 mgm. %	47.7 mgm. %

¹ We are indebted to Dr. Roegholt for the operation, which was repeated during a free interval.

The urea content of the blood A was 280 mgm. per litre and blood-sugar was 119 mgm. per cent.¹

The urine, excreted immediately after the attack, showed at every examination but one, a slight reduction of Fehling's solution. The urea content as well as the ammonia content were increased.

These chemical analyses indicate that a difference must exist in the metabolism during and between the attacks. The quotient of calcium and potassium was 1:2 during the attack and 1:7 during the interval. According to Kraus and Zondek this shifting should be related to an imbalance of the autonomic nervous system in the sympathicotonic direction. This conclusion has to be made with greatest precaution as the attack during which blood was taken was a very mild one and the analysis has been made only once. We have already mentioned that Janota and Weber emphasized a shifting in a vagotonic direction.

A chemical analysis of the blood in this disease has been reported several times and the results have always differed (Shinosaki, Kirk and Möller). Therefore we think that only an autonomic imbalance exists.

During the attack the lactic acid seemed to be twice as high as during the interval. A similar observation, even a higher increase, has been made by Kirk and Möller. In agreement with these authors we are inclined to explain this phenomenon by the diminution of muscular function. Finally, the urine excreted immediately after the attack showed a slight reduction of Fehling's solution. The blood-sugar content could be estimated only once during an attack and was found to be normal. No glucose was present in the urine after this attack. Shinosaki saw an increase of the blood-sugar during an attack, but Möller and Kirk found the blood-sugar curves during the attacks always normal.

DISCUSSION.

(A) *Patho-physiology.*—There is no definite knowledge of the cause of this disease. The chief point is that at a given moment some striated muscles lose their power of contraction. Sometimes the factors precipitating this phenomenon are known, more often they are not. We believe that the essential basis for an attack is to be found in an alteration of the chemistry of the muscles. Alteration in the chemical constitution of the blood and urine during the attacks gives a hint in this direction.

Several authors have advanced different possibilities. It was thought that for some reason the blood supply to the muscles was diminished and

¹ We are indebted to Dr. Grünbaum and his staff in the laboratory of General Pathology for the chemical analyses.

owing to this their function was impaired. Janota and Weber, however, think that if a muscle is deprived of blood supply for two or three days its function cannot return so quickly. Other authors have assumed that the removal of products of metabolism of the muscles by the lymphatics is blocked, and that the accumulation of waste products impairs the functions of the muscles. A third view is that intestinal toxins which have a selective influence on the muscle tissue are absorbed, but on this hypothesis it is impossible to explain why during the circulation of these toxins some muscles are paralysed at one time and not at another time. It has been assumed that the alteration of the metabolism of the muscles is part of a general disturbance of the metabolism; Möller and Kirk, for instance, found a marked elevation of the basal metabolism during the attacks. Since a toxic factor has not been demonstrated in the blood, the spinal fluid, urine or faeces, this does not seem to be a likely solution.

Shinosaki found in several patients a disturbance of the parathyroid gland, and suggests that the familial periodic paralysis is due to an endocrine disturbance. We found no evidence of this in our cases. A combination of several correlated factors is more probable, as an alteration of the chemistry of the muscles, a disturbance of the endocrine glands and an autonomic imbalance. We can only conclude that in subjects with a heredo-familial predisposition to familial periodic paralysis an important alteration of the chemistry of some of their striated muscles occurs for unknown reasons.

(B) *Pathological anatomy.*—Holtzapple and Schmidt report autopsies on a few patients with familial periodic paralysis in which nothing abnormal was found. Shinosaki mentions slight abnormalities in the parathyroid glands and on this based his hypothesis of over-function of these glands. Several biopsies of muscle have also been reported, but although sometimes rarefaction and degeneration of the striated fibres with multiplication of their nuclei have been described, most authors are of the opinion that these findings are not of importance. Only Goldflam found a definite alteration in the muscles fibres.

Two small pieces of the musculus rectus femoris were excised in Case 12, one during a mild attack and the other piece during an interval. Dr. A. Scholte kindly undertook their microscopical examination. One piece of muscle had been preserved in absolute alcohol and was embedded in celloidine; a second piece was preserved in formalin and afterwards embedded in paraffin. The third piece was fixed by the so-called "susa" method and stained by Heidenhain's method. As in other cases reported in the literature, no

definite pathological changes were found. A few atrophic fibres with multiplication of their nuclei were seen and here and there vacuolization of fibres which was considered to be an artefact.

So we conclude that anatomical examination throws no light on the essential nature of the disease.

(C) *Neurology*.—In the case in which we were able to observe several attacks, examination during the seizures disclosed the well known syndrome of flaccid paralysis, absent reflexes and diminished or absent electrical excitability of the muscles. In the interval between the attacks the neurological examination in this case revealed no abnormality. Of importance is the fact that in Cases 8, 9 and 10 of this report, the attacks of periodic paralysis disappeared in later life.

The development of a permanent muscular weakness in four cases of this family is a matter of great interest. Two of these cases were examined thoroughly, but in the other two cases we have only post-humous reports.

Residual weakness in members of a family afflicted with periodic paralysis has been previously described in the literature. Among seventeen cases in one family, reported by Holtzapfle, there were two cases (not personally observed) in which muscular atrophy developed in later life. Oppenheim observed in one case of periodic paralysis a slowly developing muscular atrophy, which was especially localized in the thighs and buttocks; the knee-reflexes were absent and the calf-muscles were hypertrophic. Oppenheim, as well as by Bernhardt who observed the same combination of syndrome in a father and son, described the condition as a *dystrophia musculorum progressiva*. In Case 2 of our series we were able to follow the development of the muscular atrophy by comparison of neurological records made in 1921 and in 1933. The atrophy began in the thighs and buttocks, and produced an ataxic gait and difficulty in rising from a sitting position. At the first examination (1921) the tendon reflexes were already absent. The atrophy progressed slowly and subsequently involved the musculature of the upper arms and shoulders. The distal portions of the extremities have been relatively spared, although movements of the feet are now somewhat impaired. No fibrillary contractions were observed, but there is a definite reaction of degeneration. There is a questionable hypertrophy of the calf-muscles. According to the medical record obtained from the physician, the muscular atrophy in Case 5 developed in the same way. In Case 11 the atrophy is still in the incipient stage, but the Achilles reflexes are already absent, the knee reflexes diminished, the thigh muscles weak

and there is marked winging of the scapulæ. Muscular atrophy developed also in Case 1, but further details are not available.

The atrophy of the muscles must be regarded clinically as a form of spinal muscular atrophy, although anatomical confirmation is lacking. The clinical picture in our cases is strikingly different from the spinal muscular atrophy of Duchenne-Aran (onset of atrophy in the intrinsic muscles of the hand) as well as of Werdnig-Hoffmann (infantile) type. We must therefore recognize a third distinct type of spinal muscular atrophy which occurs in connection with familial periodic paralysis. The relation of spinal muscular atrophy and paroxysmal paralysis is a problem which we feel can only find a solution in genetics.

(D) *Genetics*.—We have reported a family-tree in which all the surviving members have been examined, and in which fourteen cases of periodic paralysis were distributed among three generations. This is the first known family with this disease in Holland, and comprises the largest number of afflicted members with the exception of the family reported by Holtzapple.

If we examine the hereditary factors more closely we find, firstly, that the principle of anticipation is followed more or less accurately in our family tree. In the first generation the attacks appeared at the time of puberty; in seven cases of the second generation at the age of 7 or 8 years, while in two cases of the third generation the seizures began at the age of 4 to 6 years. There is no preference as to sex. Finally, those members of the family who are free from the disease bear progeny who are also unafflicted. The presence of migraine in some of our cases, and of epilepsy in one case, is only an indication of a neuropathic diathesis.

The appearance of spinal muscular atrophy is of great importance for the genetic relation. In the first place it must be noted that in no families with periodic paralysis have isolated instances of muscular atrophy ever appeared without preceding periodic paralysis. The question therefore arises whether this atrophy plays a rôle in the hereditary scheme, or whether it is simply secondary to the periodic paralysis. The latter hypothesis is defended by Holtzapple, who claimed that the ischæmia eventually produced a degeneration of the ganglion cells of the anterior horns and consequently an atrophy of the muscles. We cannot accept this explanation. Firstly, the development of a muscular atrophy bears no relation to the severity or frequency of the attacks; for example, in Cases 3, 8 and 12, there were frequent and severe attacks but no atrophy has developed. In

Case 11, however, the patient has had only five slight seizures and the atrophy is already appearing. Moreover, the appearance of the muscular atrophy also follows the principle of anticipation; in generation I it commenced between the ages of 50 and 60 (Case 1); in generation II between the ages of 30 and 40 (Cases 2 and 5) and in generation III about the 10th year (Case 11).

Further, in each of the three cases in which its localization is known the type and development of the spinal muscular atrophy were similar. From this we conclude that not only periodic paralysis, but also the spinal atrophy, occurs on an hereditary basis. The presence of tuberculosis in one case and doubtful tuberculosis in a second was probably an irrelevant factor.

If we now try to apply Mendel's law to our collected material, we are able to explain genetically this family history by adopting the presence of two pathological hereditary factors, both being dominant and denoted as A and B.

If one or the other factor is present then periodic paralysis appears; if both factors are combined there is also a muscular atrophy. In the first generation the oldest patient can be in this scheme most probably represented by the formula AaBb, and his wife (not affected) as aabb.

This results in the second generation in $\frac{1}{4}$ AaBb (p.p. and m.a.) $\frac{1}{4}$ Aabb (p.p.), $\frac{1}{4}$ aaBb (p.p.), $\frac{1}{4}$ aabb. (healthy). We have seen in the second generation that eight of the twelve children (one child died in infancy) suffered with periodic paralysis and that two of these eight were also afflicted with muscular atrophy. Third generation (children of Case 5) shows the same distribution as in the second generation; there are four children, two of which are suffering with period paralysis and in one case also with muscular atrophy.

We realize that the information derived from one family is not sufficient evidence to establish a theory. An application of our hypothesis to the cases described in the literature is unfortunately impossible because of the scanty hereditary data available. Tracing a family lineage in a thorough manner is often fraught with difficulty; this may explain the paucity of reported instances of combined hereditary diseases such as we have described. More extensive investigation of such families is desirable, and we hope that it will produce the evidence necessary to fortify the hypothesis of the two dominant factors.

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AN ANALYSIS OF DISTURBED FUNCTION IN APHASIA.

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WITH Broca, Wernicke and Liepmann there developed in Germany an exaggerated view of the importance of cerebral localization. This was less pronounced in England owing to the influence of Jackson and of Head. The work of Goldstein [1] has been the impetus to a new approach to the problems of aphasia and of cerebral localization in general. Following him a number of other workers have entered this field, Bouman and Gruenbaum [2], Woerkom [3], Wolpert [4], Jossmann [5] and others. Their approach has been largely influenced by more modern psychological views, particularly Gestalt Psychology and Phenomenology.

Methods of observation had hitherto assumed, falsely, that vital processes are in themselves psychological or physical; hence the failure of attempts to combine material so gathered. Vital processes are integrated, and a common basis for dealing with the material obtained by observation would lie in an approach that is neither purely psychological nor physical, but concerned rather with material that is not specifically either. Analysis of function and related structure serve this purpose.

A considerable amount of material has been gathered in this way by the above-mentioned authors and others and it will be referred to below. It was for the most part obtained by the extensive investigation of single cases, those points being more closely inquired into which were apparently unrelated to the main symptoms of the illness. It is the close examination of these details, formerly frequently overlooked, that has proved fruitful in the investigation of function. It will be seen, then, that the complete investigation of the single case is more important in such a method than the discussion of a number of similar cases, where in practice difficulties arise through the consideration of adventitious differences.

¹ This work was done during the tenure of a Commonwealth Fund Fellowship at the Maudsley Hospital.

The case to be described is intended to indicate the value of an individual examination conducted from the point of view of function analysis, and brings to light some fresh conclusions.

Case: F. W., aged 43, was a commercial traveller before the War, in which he served as an officer in the Air Force. In France in 1916 he was wounded in the left leg and gassed. After eight days in a field hospital he was discharged fit. He remained in the Air Force until 1919, when he fell from an airship at the moment of landing. He was in hospital for three weeks and says that he lost his speech for a short time after the fall. In the same year he was demobilized with a gratuity. About once every year after this he had sudden attacks of giddiness which passed into unconsciousness, and following which he was unable to speak for about twenty minutes. After demobilization he went to India as the agent of a large firm. In 1924 in Bombay, though apparently in good health, he collapsed and became unconscious in the street. He was taken to hospital and lay there three weeks in an unconscious or semi-conscious state. When he came to he was paralysed on the right side and unable to speak. The doctor who treated him then reported:—

"I found on that date that he was suffering from aphasia, resultant on hyperpyrexia of three weeks' duration."

A certain diagnosis of the cause of the fever and the cerebral lesion could not be reached. There was no question of malaria. After a few months he was sent back to England and spent the next eighteen months in hospital. At the time of his discharge his speech and particularly the paralysis had improved, but had been stationary for the last few months of treatment. Examination of blood and cerebrospinal fluid in 1928 gave no indication of lues.

Present clinical findings.—Nothing abnormal in chest or abdomen. A round scar, freely movable, over the left parietal bone, $2\frac{1}{2}$ cm. in diameter, three fingers' breadth from the parieto-occipital suture, and two fingers' breadth from the midline. X-ray: an old fracture running sagittally through the left parietal and extending into the occipital bone.

Neurological findings.—Pupils and cranial nerves normal. Slight diminution distally of touch, pain and temperature sensibility on the right side. Joint sense normal everywhere even for the finest movements. Localization: normal with left finger on left side, slightly inaccurate with left finger on right side, with right finger on either side 5 to 6 cm. out, with the right finger on the left arm grossly inaccurate.

Muscular power a little diminished in the right hand. Individual finger movements in the left hand were quite normal, as also in the right except for occasional concomitant complex movements of the other fingers. Spontaneous voluntary movements on both sides were quite normal.

Abdominal reflexes on both sides present and equal. Plantar reflexes showed a right Babinski. No other neurological signs apart from the aphasia.

There were no signs of any affective disorder, so often characteristic of cerebral injuries, or of any other disorder of the mind.

The patient was quite conscious of his failings. He was always ready to submit to daily examinations, often lasting for hours. It is significant that signs of fatigue were late in onset and slight in degree. When he failed in a task he rarely showed the "catastrophe reaction" in the form described by Goldstein. Conversation with him was restricted to superficialities; he was unable to follow anything difficult.

Speech.—Generally speaking the patient showed an amnesic-aphasic disturbance with much verbal but also literal paraphasia. In spontaneous speech his sentences were very simply constructed. He only used the most indispensable words. Words with a temporal significance, e.g. "after," "last," "quick," &c., were well preserved. Most words with a spatial significance, e.g. "over," "upon," "below," "at," were practically never used, but a few of these, "back," "to," "down," were used often and equivocally. Otherwise, when occasion demanded the use of such words, he had recourse to gesture.

His vocabulary was poorer in abstract than in concrete nouns. Some words he was capable of using at all times, others sometimes only, and many he used practically never. The length of words played no part in this. His vocabulary was smaller in experiments than in spontaneous speech. In the use of words he tended to make slips, usually belonging to the same sphere of ideas (*cf.* Pick [6]), i.e. using words related in meaning or category. What this sphere was depended on the circumstances.

In naming objects, he found it easier to indicate the activity connected with them than to recall the name itself. But he did this more easily if the object was shown him, or its use demonstrated by characteristic movements. Errors in naming objects amounted in the first examination to 40 to 50 per cent. The sphere in which the slips were made was often an optical one, in a wider sense; thus he confused cup, plate, drinking-glass. Mistakes of a different kind were "hoses" for fountain, "Christmas" for mistletoe, where the relation in meaning is obvious. He showed a peculiarity which will be discussed in detail later; sometimes he found the name of an object at first showing, but was unable to do so when it was shown again after three or four others:—

<i>Necktie</i>	...	...	...	named immediately
Stove	...	...	...	after 1 second
Safety-pin	...	...	...	" " "
Sand	...	...	...	immediately
<i>Necktie</i>	...	...	...	after 5 seconds

Flower	...	...	after 1 second
Leather bag	...	...	immediately
Coal	...	...	"
Knife	...	...	"
Necktie	...	...	not at all.

Although able to describe former experiences vividly, his speech was poor if he was asked to describe some object in detail.

For instance, he was asked to describe a locomotive: He said, "Well, I told him. See engine, buffers, . . . steam, coal, . . . 'lectric and a driver and second driver. . . . The engine driver his job for steam to take for 'nother station." But how does such an engine work? "Engine is a steam and power."

The lack of small words conveying the direction of movements is well shown in the following examples:—

(1) A match was put through a hole in a piece of cardboard. The patient says: "You letter open to the pin or match."

(2) A leather bag is taken from a chair below the table and put on the table. He says, "Leave it, the bag the chair, then you give it your bag table."

For the most part, when the right word was given by the examiner he caught on immediately, nodding and repeating the word and rejecting other wrong words. However, in the case of such words as "through," "at," "under," &c., he remained undecided and usually accepted whatever was given him first. In enumerating a series, he tended to slip into the wrong series. Thus, he began to count when he was asked to give the months. The ABC, however, was always given quickly and correctly.

In the course of the next three to four months, he improved considerably. This is remarkable, as his speech had been stationary for the last six years. At the end of the period of examination, March, 1933, errors in naming 200 objects in pictures amounted only to 15 to 20 per cent. This was uninfluenced by the introduction of entirely new objects.

Repetition of sentences spoken by others was much disturbed. Sense-related paraphasia was prominent and literal paraphasia also occurred, e.g.

He was asked to say, "Tom had to go to his grandmother." He said: "Jim was . . . the grandmother."

Again: "He appealed to his charity," became, "Charity . . . his help."

As Goldstein has pointed out [7], the ability of aphasics to understand speech is less well preserved than is often assumed. This patient, who did not show a strictly limited form of amnesic aphasia, had many difficulties in understanding speech. In a superficial conversation he appeared to understand well, but if the subject was quickly changed he became slower and always kept an attentive eye on the speaker. It was discovered that it was often a few words that conveyed the sense of the whole more or less correctly. He did not notice words arbitrarily and nonsensically inserted, especially if in a sphere of meaning such as he himself might deviate into.

In the understanding of speech he was considerably influenced by the gestures of the speaker. This was particularly noticeable in sentences making use of such directional words as "upon," &c. Words which did not involve gesture were often beyond his comprehension. The patient himself was quite unaware of his roundabout methods of understanding.

It might be expected that the comprehension of individual words was more difficult than that of an entire sentence. Goldstein has pointed this out and has explained it on the basis of the Gestalt theory. Experiments were made in this connection with 200 words, nouns, verbs, pronouns, &c., the time of comprehension being measured with a stop-watch. It was found that words he understood at once often showed a close affective relation to himself or to his memories, and the words he failed at were those like "through," "among," &c., where there was no such relationship.

In the course of the examination period, a striking improvement in this experiment was noticed. In the first experiment of 200 words, ten were not understood at all, sixty-two were understood immediately and the remainder required 260 seconds. In the last experiment, after two months, with new word material, he failed only in seven words. He understood immediately and correctly 123; and the remainder only required 126 seconds.

He read the ABC without a mistake, saying it to himself aloud. Asked to read the individual letters, he read A, the beginning of the alphabet and F, his own initial, immediately. Other letters caused more difficulties. He made slips owing to acoustic similarity, e.g. P instead of B, or slips caused by neighbourhood in the alphabet, e.g. L for M, and R for S.

The explanation seems to be that the ABC was more a unity for the patient than individual letters and so it is understandable that he

produced the rarer letters Q, X and Z, more quickly and accurately than E, M, O, &c. The lesser-used letters preserved for him a more individual character than the others, which had lost it by constant use in the most varied words.

In writing letters he showed a special localized factor which will be described in another context. For instance, asked to write several times a series of twelve letters, his writing became progressively slower, but, if a new series of twelve letters was used, the first few lines of the new series were as quick as the first of the old. An interpretation of this will be offered later on.

In copying written or printed material he made comparatively few mistakes, but he copied mistakes or nonsensicalities along with the rest, and usually understood very little.

Sponstaneous writing was practically impossible except for his own name and the names of certain towns. To dictation he wrote only a few short words correctly, those which he understood at once and used himself in conversation. The mistakes in writing to dictation were of the same nature as those made in talking, literal slips and slips related by meaning being frequent. Thus, he wrote "mother" for "marriage," "gods" for "heaven," &c. In the following sentence every word shows such a slip: He was asked to write, "I can write anything." He wrote, "We may letter another." Usually, however, his results were even more corrupt. Thus, he was asked to write, "My friend sold his dog," and wrote, "He it at's work's." It is worth noting that in a sentence the approximate number of words, and in a word the approximate number of letters, were always correctly retained.

In the case of an amnesic-aphasic patient, Lotmar [8] described the occurrence of "intermediate experiences" between the perception of an object and the production of its name and considers the errors appear during these experiences. In our patient, also, such intermediate experiences were found, occurring both before and during the writing of single words. As writing requires more time than speech and as the intermediate experiences continue meanwhile, the relation between what was asked for and what was written was not often visible at first sight; but often the patient, by describing what had "entered his head," gave a clue to its comprehension. Of course, he had to be trained to recollect all these intermediate experiences. What he wrote was always covered up immediately and he hardly ever remembered what he had written, so his statements as to intermediate experiences may be accepted as reliable. The following are some examples:—

Dictated—Hungry.*Written*—Round-s.

Patient's report: I saw far away; he lost his place, there no houses, forest—is a man go *rounds* for the shops, all places for orders. Woman waiting for the foods, *hungry* for food.

Dictated—End.*Written*—Down.

Patient's report: End, fear, devil, hell (patient points downwards) . . . same thing.

From the point of view of function analysis, the essence of any mental event is best understood by using Goldstein's conception of figure-background relation, largely drawn from Gestalt psychology. The "figure" is the content of the individual happening. The "background" is the substratum on which the formation of a figure takes place. The figure stands out with a definite structure in relief against the background. The "tendency" is the active factor, producing the figure out of the material of the background. It is selective in its action, taking those elements which are most suitable for the formation of the figure, and, on the other hand, rejecting what is not suitable. The aim of the whole process is a figure formation as precise as possible. I have discussed elsewhere [9] how the patient's defects may be understood by these conceptions.

When normal people are poisoned with mescaline [10], there is in every directed act of thinking the emergence of loosely related material from the background. This material, becoming more and more obtrusively clear, interferes with the unitary directness of the thought process. In other words, the formation of a precise figure cannot occur.

Something similar must be assumed to occur in the case here presented. The patient is at the mercy of loosely related material from the background, which disturbs the precise formation of a figure. This becomes particularly clear when a word is changed out of all knowledge, but where his subsequent statements allow one to see how it was produced, e.g.

Dictated—Painter.*Written*—Piarets.

Report upon intermediate experiences:—

Picture. "I see big picture in Egypt. I know I have been there. I see picture in a book. Arabs, Port Said, horses."

On the word "painter," the sense-related complex "picture" emerges, the first two letters of which are written down; then it becomes a definite picture with "Arabs" seen in a book. Here again, two to three letters are written down joined to those preceding. At the end, the form "ts" probably originates from "Port Said." It is seen that in

writing the patient shows a disturbance in principle identical with his paraphasic slips in conversation. Only in writing the process appears in slow-motion, as it were.

Reading.—The reading of single letters was fairly good. A, B, C, D, E, F, S, T, W, were recognized immediately. These are the first letters of the alphabet and the first and last letters of his own names. Apart from these letters, whose optically privileged position is evident, he had to recognize others by orientation from the alphabet as a whole, i.e. by reciting it to himself. The reading of single words was prompt but with frequent mistakes. These seemed to be caused preponderantly by optical similarity. Thus, he read "national" for "material," "immediate" for "imitate," &c. The beginning of the word seemed to be the decisive factor.

Comprehension of reading was slower than that of speech; but here also in the course of time a considerable improvement took place, independently of reading exercises. The reading of texts showed mistakes produced not only by optical similarity, but also by the intrusion of sense-related words. Comprehension was thereby made extremely difficult and was confined for the most part to single impressive words or short frequently occurring phrases. Comprehension was better if he was allowed much time for reading and was able to repeat the text several times to himself, and when the text was not too long, e.g. in the form of short orders or instructions.

It is reasonable to suppose that the patient had to make a fresh attempt to understand every new word; for as the comprehension of the first words was delayed, they would give him no help with the comprehension of those following. This is probably the reason why there was a general tendency to make optical errors with longer words, and sense-related errors with phrases.

The writing of words read tachistoscopically.—The patient had to write the word immediately, whether he understood it or not, and then to recollect his impression of the original. It was the words he had not understood that he wrote most correctly, e.g.

<i>Exposed</i>	<i>Written</i>	<i>Read</i>
Down	Down	Low
Piano	Peones	Piano

In other words, where he was left to the optical impression alone he wrote quite correctly or nearly so; but where he understood the meaning immediately the resulting intermediate experiences led him astray.

Calculation.—The meaning of the symbols of addition, subtraction,

multiplication, &c., was completely lost, but he could read and write correctly numbers of four figures. He understood, however, that in a simple calculation numbers separated by one of the signs ($\times$, $+$, $-$) were to be united into one, but the mistakes he made could not be accounted for only by the loss of these symbols, e.g. his answers to the calculation " 3×2 ," which was put to him 13 times, were, 3 times "8," 4 times "6," 5 times "8," and once "11." It was found that when the patient read the problem, the correct answer, i.e. "6," immediately came into his mind. But he had lost the knowledge that such an automatic response was an answer to the problem. These solutions are learnt at an early age, and are not for adults a thinking process, but have been fused long ago into a single whole, " $3 \times 2 = 6$ "; whereas the patient identified the solution with, say, the first part of the problem and then began what was for him the solution proper, by adding or subtracting the second part. Often he added both parts together again to the result.

He was better at applied problems that did not involve the use of a mathematical formula. In dividing a heap of pebbles into a number of equal heaps, he proceeded with numbers of 9 and over empirically, i.e. by taking 2 or 3 away at a time. Presented with numbers arranged in a definite series which he was asked to continue he found greater difficulty. He proceeded empirically, by feeling his way as it were, and did not understand the nature of the series intended.

Time sense.—The patient was capable of dealing with ideas involving time in concrete instances, but it was found that the conception of an "objective" or "abstract" time was beyond him, a point to which Woerkom [11] has drawn attention.

Drawing.—The patient had once been able to draw quite well, but now his drawing was no better than that of a child of five or six. In drawing from memory, the difficulty was the greater the fewer the striking features offered by the object. He confused such geometrical figures as a circle, cross, triangle, &c., though his difficulties in the understanding of words were not involved. Asked to draw a plain sketch of the Day Room of his ward from memory he forgot nothing, but drew in everything as he would meet it going through the room in his mind, but everything was out of proportion and unconnected. Other objects he drew in the position (mostly profile) in which they present themselves to the eye most impressively and was unable to change his point of view, e.g. he could not draw a carriage seen from behind or above.

Comprehension of pictures.—He grasped the meaning of a picture only superficially and usually occupied himself with irrelevant details, except where only one or two persons were represented in expressive action or, better still, in a series of pictures in which the action was continuous. Jossmann [12], describes a similar condition in the case of a patient with optic agnosia and he says that in such cases there is a loss of "Bewegungsmotive," literally movement motives. By this one understands everything in the way of bodily movements, especially of the eye muscles, which has been experienced during previous visual or spatial perceptions. They also imply the possibility of projection of the definite form of such movements into the outer world. In his attempts to understand pictures and in his drawing, the patient showed a lack of "Bewegungsmotive"; and we may say, as Jossmann does, that the patient's performance becomes easier where, with regard to the "Bewegungsmotive," he receives assistance from the object, i.e. where the latter was in movement or use.

In some experiments, the patient was given a map of Europe to look at. Gestalt factors played a part here. He recognized Europe immediately, but of the individual countries, only England and Ireland. Characteristically he tended to confuse Italy and Scandinavia.

Vision.—Visual acuity was normal. The seeing and discrimination of forms and colours showed nothing abnormal. Even if these were presented tachistoscopically there was no failure. However, in drawing something he had seen he often mixed up top and bottom or left and right. Retention of a definite form or colour, of which twenty-six tints were employed for two or three minutes, showed no errors.

Visual imagery.—Although this was certainly possible as is shown by the retention of colours, yet in imagining a definite object he often failed to find the right colour. Further experiments showed that he linked every object with a colour but very frequently with the wrong one. Thus, asked how he imagined a sword, he pointed to red; a fox, to grey-lilac; straw, to green, &c. As intermediate experiences can be excluded here, there is only the explanation that the relation between form and colour of an object has become very loose.

His visual images were sharp, and he could always report numerous details. In imagining simple forms there was a tendency to make them more concrete, and so richer in sensory qualities. In imagining simple objects, he could retain them unaltered for a much shorter time than the normal person. If the visual image vanished from his mind's eye he could not regain it of his own volition but succeeded in doing

so if it was recalled to him by the examiner. There was a tendency in imagining a single object to enlarge it into a whole scene. Normal people show the same tendency in attempting to imagine abstract figures, and it appears to make the image more stable, as it adds to the sensory content.

In picturing small incidents told to him he usually diverged considerably, but the new contents were never senseless but only represented another possible development. The same principle was met here as was found to underlie the disturbance of writing. Asked to imagine the same story while it was being told him, no divergence occurred. We find here, as in picturing single things, the help he obtained from direct reliance on what was said to him. If he tried to imagine objects in action, he could only do so when accompanying them by movements of his head or eyes. If this was prevented, or if the character of the movement to be imagined did not permit of this, he was unable to imagine such a movement, but saw the object asked for in repose or in various successive positions. This is an unequivocal proof of what has been said about the absence of "Bewegungsmotive."

Experiments with visual imagery were performed with the aid of a turning wheel. The effect of this was to produce a moving after-image. He was then told to imagine an object moving in an upward direction, whilst the pseudo-movement produced by the wheel was downward. In the normal person, these pseudo-movements have very little effect on movements of the image, but in the patient the immediate effect was to make the imagined object move in the direction of the pseudo-movement. However, the movement, added in this way to the image, gave an added clarity and distinctness.

Evidently the patient is hardly able to imagine movement at all. Spontaneous images when he sat with his head fixed were always devoid of movement. In this connection it is interesting that since the onset of his illness he says he has had practically no dreams.

Auditory performance.—Clinical examination of hearing showed nothing abnormal. Sound discrimination was very good as also was the localization of the source of a noise. He played the piano by ear quite well, even tunes that he had heard for the first time in the last few years. He was able to transpose melodies from one key into another without difficulty. He played with feeling and without errors in harmony, yet the rhythm was wrong. A march sounded like a waltz. The patient similarly made mistakes if asked to beat out a simple rhythm. In other words, in the auditory field we find the same

deficiency of "Bewegungsmotive" as in the optic field—most clearly shown where they are tested in as pure a form as possible. However, here, as elsewhere, there was not a complete loss, though a profound deficiency. He could beat out even a difficult rhythm after prolonged training. In a similar way he succeeded in repeating difficult words such as "hippopotamus," or even entire sentences, without mistake at the first attempt with the aid of such training in rhythm.

From the point of view of function analysis, the same conditions prevail here as where the patient found it easier to name an object if the characteristic action was given him, or to imagine the action whilst it was being described or accompanied by movements of his head or eyes. The common factor is an enrichment, a performance no longer restricted but receiving help from various sides.

Auditory imagination.—The patient was unable to imagine sounds or voices. Asked to imagine a scene in which there was sound or speech, he could picture the optical elements but not the auditory; but he could imagine a song with the accompanying words. It was found that he accompanied the song by movements of the larynx. Characteristically he could not imagine a whistled tune. He was able to imagine sounds after they had been produced. He could imagine the sound of a running water-tap eight to ten seconds after it had ceased, during which time the auditory image became weaker in his mind. Any low indistinct noise helped him to imagine sounds of his own choosing. The gentle crackling of coal in the grate produced the image of the noise of a falling poker; when the table was lightly scraped, he pictured the noise of a falling table.

Until these experiments the patient had been unaware of his lack of auditory imagery. A restriction of perception must be assumed to be present, though it almost evades clinical examination and only clearly appears in the imaginative field. Here also at the end of the period of investigation considerable improvement had occurred, so that even without the aids mentioned, he could sometimes succeed in imagining voices speaking a few words.

Tactile sense.—Von Frey's hairs of a flexion weight between a few milligrammes and 2 grammes were used so that the results of examination could be compared with objective standards. Wide areas, 7.7 cm. diameter and more restricted areas, 5.5 mm. diameter, were stimulated over a wide range. The first provided information about the general condition and changes in function, the second about fatigue phenomena. There was diminution of sensibility not only on the right side but to a

lesser extent on the left, most pronounced in the arms. With every resumption of a series of stimuli it always required some time for the patient to feel a stimulus for the first time. An interruption of only forty seconds was sufficient to produce this phenomenon afresh. It held true even with fairly strong stimuli and was independent of the tempo and rhythm in which they were applied, and was true for both touch and pain. This increased difficulty of adaptation at the start of every series of stimuli is not explicable by a disturbance of attention, for it showed itself even if every stimulus was applied under the eyes of the patient, though the average value of the series was a little better under these circumstances. This shows how sensory enrichment improves the performance without interfering with the principal factors in the disturbance.

Here, as elsewhere, improvement occurred. The increased difficulty of adaptation at the start of a stimulus series became gradually less and the average values better. There is, therefore, a level of sensibility, low at the start of every demand made on it, but rising during the period this demand is being made. There is, further, a general rise of the level during the period of improvement which is independent of individual demands.

In the tests of fatigue in restricted areas, signs of fatigue regularly appeared, but they did not irradiate into the neighbouring areas as is frequently the case with central lesions; on the contrary, the neighbourhood of the fatigued area showed a better average value after the test than before it. This improved value was found for two to three minutes after the test and decreased gradually outside a radius of about 10 cm. A similar improvement could be found on a symmetrical area on the other side of the body without the latter having been stimulated.

The strict isolation of the fatigue area from this neighbourhood permits of the conclusion that there is a tendency to improvement in the restricted area itself, but that this improvement is annihilated by the fatigue. I have discussed the fact of irradiation on the opposite side in an earlier paper [13].

These results may be regarded from the point of view of function analysis as follows:—

The perception of stimuli is the emergence of a figure from the background. At first this was not possible in the patient owing to the increased difficulty of adaptation. Later not only the stimulated point emerged, but simultaneously there was a rising of the level of the immediate neighbourhood. From the point of view of function analysis

this irradiation may be regarded as dependent on the unprecise formation of too broad a figure.

From this it would appear that all points within this wider figure have the same value for the patient. This is not difficult to show in the case of the skin, for the patient localized spots stimulated by pressure very inaccurately, erring by 3 to 7 cm. Further, if with his eyes shut, he was asked to bend a finger touched by the examiner, he generally bent the wrong one, but did it correctly when the finger was not touched but named. Owing to the preserved visual image of his fingers, there was still a possibility of a response not to be elicited through the tactile field.

These findings cannot be interpreted simply as a reduction of sensibility as a *state*, but only as a *functional* disturbance in the figure background relation. This is shown by results of tests of stereognosis. His errors in these were always in a related field, and never completely incomprehensible. Thus, for example, he called pumice "soap," rice "peas," a brush "comb," &c. It was found that he really believed he had had these things in his hand, and his errors were not due to the aphasia. On the contrary, these disturbances, together with the aphasia, have a common explanation.

The errors in the same field, the increased difficulty of adaptation, the intermediate experiences, all belong to the background of the desired figure formation. With the patient they tend to enter the figure formation; thereby all details in this figure formation are equalized and in their value to him one is the same as the other.

Tactile imagery.—At the beginning of the period of observation, he was unable to imagine any touch, pain or temperature on his arms or legs. He could do so on other parts of his body, but only more slowly and with greater difficulty than the normal.

Towards the end of the period of observation, this imaginative ability gradually returned in the arms and legs as well as the trunk, in the same measure as the improvement of sensibility itself. With each test ten to twenty seconds was required for him to "feel in his mind" what was asked, and with each renewed request the imagination became clearer. But, even before this improvement had been attained, he regularly succeeded in producing such images, e.g. that he was being touched by a brush when this was shown him, without it, of course, being allowed to touch him. It was found in a number of examinations that after such tests of imagery, tests with the stimulating hairs showed a considerably improved value for the corresponding parts of the body.

This shows that when he directs his imagination to a definite part of the body, sensation is improved there. This influence also extended to the corresponding spot on the opposite side, but not to other parts of the body.

Movements.—Movements called for by the situation in which he was placed showed no abnormality. His well-preserved gestures have already been mentioned, but the picture changed when he had to act, i.e. carry out characteristic movements without the appropriate object. Disconnected and wrong movements occurred at first every time, but gradually disappeared with repetition until he succeeded in getting the right sequence of movement.

Another striking point was that he was unable to carry out different movements simultaneously with both hands without an object. The movements interfered with one another and the final result was that he carried out approximately the same movement with both hands.

The same disturbance in principle is found in movements as in sensation, the same increased difficulty of adaptation and slowness before the development of the correct performance, the same influence of one side on the other. Here also in the course of time improvement took place.

The imagination of movements of his own body.—When the patient was asked to imagine a scene in which he himself played a part, he was rarely able to picture his own activity. Almost always he imagined his role as performed by someone else. The only times where he said he could do it were occasions when the choice of content was left to himself and he went back in memory to scenes he had actually lived. Later it was possible for him to imagine simple movements of the arm or leg, but even here ten to twenty seconds were required for such a performance to become possible.

Measurements of reaction times.—Thanks to a suggestion of Dr. Golla, the measurement of reaction times was effected with an electric clock. The patient was required to press on a contact immediately after a strong tactile stimulus to his back. The average values of forty to seventy individual experiments showed no great difference whether the stimulus was applied to right or left side, but the values obtained when the making of the contact was by the right hand were considerably higher than with the left. At the beginning the first values of each series were extremely high ($700 \pm 1,100 \sigma$); but in the course of time, the average values of both sides improved steadily, until eventually

there was no difference whatever on the part of the body to which the stimulus was applied.

At the beginning, average values for the left hand were 360 σ , for the right 550 σ ; at the end of the period of examination—250 σ left and 370 σ right.

Summary.—From the history and clinical findings the patient must have a lesion of the left posterior temporal area. The most likely cause is a late post-traumatic hæmorrhage. This localization is in consonance with Goldstein's findings of the localization of the lesion in cases of amnesic-aphasia on the basis of his collected experience [14]. On the basis of general figure and background relationships, the following peculiarities were shown:—

(1) Unprecise figure formation in which sense-related or Gestalt-related material tended to intrude.

(2) An increased difficulty of comprehension of details, along with an easier grasp of the complex. Conversely an increased difficulty in the solution of complexities.

(3) Lack of "Bewegungsmotive." It shows itself in speech in a general absence of the small words conveying spatial and temporal relations.

(4) Rapid fatigue of a special kind shown in certain exercises.

(5) Increased difficulty of adaptation where there was not complete loss.

(6) A general tendency to improve occurring over the total period of examination and entirely unspecific, i.e. showing itself in forms of behaviour in which there had been no practice.

It is the aim of this paper to understand these on the basis of a common functional disturbance. For this a distinction must be made between the form of a function and the contents or material of a performance. In dealing with the latter we are obliged to adopt a psychological or physiological view-point, but with the former a neutral attitude can be assumed. As is most clearly shown in the experiments on tactile sensibility, the disturbance of function can be understood as follows:—

Wherever performance differs from the normal it is at a lower level. This lower level is the basis for many types of performance but will differ in different fields.

Performances starting from this lower level have to be regarded under three heads: (1) Where the performance is isolated. (2) Where it is complex. (3) During the course of improvement.

By isolated performances are meant those which are not the natural result of the situation in which the patient is placed and those which lack all help from sources outside the task itself. In these performances there is firstly, a delayed start; secondly, performance is diffuse, i.e. the figure formation is unprecise and too broad. Thus performance is equivocal. Where a sufficiently precise figure formation is attained gradually or immediately, the process proves to have a specific fatigability (for example, where the word necktie was asked for several times, where the same series of letters had to be written several times and where the fatigue phenomena in stimulation of restricted areas of skin were investigated).

Most of the spontaneous performances were not isolated but complex. By these are meant all those involving several sensory systems or qualitatively different material taking part in the figure formation. In practice, the difference between isolated and complex performance is often a matter of degree. A performance demanded by the situation is, as a rule, very complex, as it is one that can hardly ever begin and end in the same sensory system. It may be said in general that the more sensory material involved in any performance, the more precise is the resulting figure formation. It was possible to show this in performances which could still be called isolated, e.g. when the defect in performance was compensated by the provision of specific help (movements of his own head or eyes as an aid to imagination of movements, movements of the larynx when imagining song, demonstration of the use of a brush as an aid to tactile imagination, and the possibility of acoustic imagery during or in sequence to actual noises).

In a certain sense, the possibility of complex performance rests on the same basis. The greater the sensory enrichment and the more sensory material entering from other sensory systems, the more precise is the performance (e.g. the patient finds it easier to name an object when its use is demonstrated; to repeat a difficult word or even sentence if he has practised the appropriate rhythm; to solve a calculation in applied and concrete terms than in figures; to bend the correct finger on demand when this is done by aid of the visual image; or to follow conversation when he can rely on the gestures of the speaker).

The following rule can be deduced. The more complex in this sense the action, the lower may the general level of performance be without prejudice to success.

Certainly there is a difference in the formation of the figure in the cases of isolated and complex performances. In the isolated perform-

ance it is a matter of raising the functional level around the figure formation aimed at. This entails either a slowing down or an increased intensity of experience during successful performance. But in the case of the complex performance, which is facilitated by an enrichment from other systems, these characteristics are absent. It seems as if these performances can be carried out directly from the lower level.

Performances involving abstraction have to be considered separately. They are not isolated performances as their substratum is not confined to a single sensory system. They are, rather, complex performances, as they are based on several sensory systems; but they are peculiar in that despite their complexity they lack the possibility of sensory enrichment, as their essence is a departure from the senses.

During the course of this paper the patient's deficiencies in imaginative activity have been brought into direct relation with the perceptive performance in the corresponding sensory system. The relation has been shown to be direct in that imagination is most easily possible and remoteness from sensory elements most easily attained where the corresponding field of perception is least disturbed and vice versa. Thus, the imaginative faculty was at its best in the optic field, worse in the tactile and auditory fields and worst in the field of motion. In the field of movement we can best see the degree of remoteness from direct sensory experience that must be attained for abstraction processes to be possible.

The effect of the lack of "Bewegungsmotive" can be traced into the patient's speech disturbances, where he both misunderstood sentences containing the words "below," "through," "up," &c., and had lost the use of these words.

Lastly, the conditions of improvement have to be discussed.

By the performance level is understood the sum of the possibilities within one sensory field upon which a performance may be built. The height of this level is not only conditioned by the situation and nature of the lesion. What was found in the patient of "engrams" or "recollections" was to a considerable extent also conditioned by the original level of the pre-morbid state. The conception of "level" here is the purely static side of what Goldstein calls background; the latter term includes in his nomenclature something of "activity."

The background processes thus contained varied influences from several systems, but if the levels of these systems are different, then the background processes, and thereby also the figure formation, receive a peculiar stamp. The influence of the background on the figure can

be shown in the performances involving sensory enrichment (e.g. in conversation the patient relies on gestures and fails to notice arbitrary nonsensicalities; in auditory imagery the content is determined by gentle actual noises; in imagining an object in motion the direction is determined by "pseudo-movements").

The mutual relationship of the various levels was fairly constant. The point that a rise in level in one field attained by training is accompanied by improvement in other untrained fields is fundamental for function analysis.

The essence of the improvement probably corresponds in principle with that of any process of learning. In such cases as this the level is below normal, but has not lost the possibility of being raised by demands made on it.

This raising of level originates in the isolated performances. At first it is circumscribed but later is accompanied by an increasing rise in the general level, as is clearly shown in the experiments on tactile sensibility.

The limitation of the rise in level to the isolated performances explains why spontaneous improvement in such patients is slow and limited in extent. Of his own volition the patient avoids such performances; they no longer belong to his "changed milieu" (Goldstein). Rather he prefers, for the most part, complex performances conditioned by the situation. A detailed examination lasting a few weeks constitutes a fruitful and varied training for these potential abilities.

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SENILE PLAQUES.

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MUCH has been written of late about senile plaques, but nearly all the problems concerning their structure and their genesis are yet unsolved. As we find the most contradictory views expressed by competent investigators, we must conclude that our methods of research are still inadequate.

I therefore tried to investigate these problems by a method other than is generally followed. I was strongly impressed by the fact that the senile plaque is not the only histopathological alteration that can be found in the brains of those who have suffered from senile dementia. Other changes in practically every case are ; (a) the neurites of some of the Purkinje cells in the cerebellar cortex show torpedoes (local spool-like swellings) ; (b) some ganglion cells of the cerebral cortex present Alzheimer's type of fibrillary change ; and (c) some of the neurites in, or in the immediate neighbourhood of, a senile plaque show knots, buds, eyes, a simple splitting up of their neurofibrils, or a pathological increase of argyrophilia.

The occurrence of these three types of alterations in senile dementia is not a new observation, but the fact that the torpedoes and the Alzheimer fibrils are extraordinarily frequent in this disease has not been noted by other investigators and I have had to rediscover the knots, buds, eyes, &c., since little attention has been given to them in modern literature. A possible relation between these different lesions and the plaques has never been discussed in detail.

The analysis of the senile plaques themselves with the aid of up-to-date microscopical technic being insufficient to give us an insight into their nature, I put the question : Which characteristics are common to the plaques and to the three above-mentioned pathological alterations ? Such characteristics, common to all the changes developing in this disease, might give us an idea of the nature of the influences that affect the brain of the senile dement.

To obtain a clear understanding it is necessary that first a short description be given of each of the four alterations mentioned above,

and of the conceptions of their nature. After that we will be able to discuss the characteristics common to these four lesions.

Senile plaques.—Senile plaques are so well known to histopathologists of the brain that no detailed description of their general appearance is needed. A sphere 20 to 60 μ in diameter, showing in silver impregnation preparations a multitude of irregular argyrophil clumps, and in the centre of many a fairly homogeneous mass in form also a sphere, the periphery of which in most cases has radial striations. In the immediate neighbourhood of this central mass the irregular clumps are usually less abundant than at a greater distance from it, where they have a tendency to a radial arrangement. In the outer zone of the plaque the arrangement of the clumps is very irregular, perhaps rather more tangential than radial.

Numerous views have been expressed on the origin of these plaques. Nearly all the known elements of the central nervous system are considered by different authors to be their origin. In the earlier literature the view is often expressed that the plaque originates from an altered ganglion cell; later different types of glial cells were considered to be their source.

In other conceptions the plaque develops from the blood-vessels, or it is built up by pathological substances coming from degenerating cells in the neighbourhood. The confusion is increased by the fact that one and the same author has at different times expressed different views.

And in the more recent literature numerous facts which were recognized in the older literature are not mentioned. It is perhaps under the influence of the new conceptions that these earlier observations are forgotten. I myself thought that I had made new discoveries during my examination of the last ten brains, but afterwards found that they had already been made by Fischer, Marinesco and Simchowicz. Fischer, for example, spoke of severe alterations of the ganglion cells, with irregular clumplike deposits, and shrivelling up and disappearance of the processes, being found in those parts of the cortex where the plaques are most thickly distributed. The greatest change in the cells is found in the parts of the brain where the cortex is diffusely infiltrated with thready masses, and is especially great in the ganglion cells directly surrounded by these masses. At an earlier period of my own investigations, drawings show that I then considered the possibility of the plaques having arisen from the ganglion cells. Bonfiglio [3] in 1908 thought plaques were formed in this way, but in 1921 he admitted that it was not so in all cases (see Divry [6]).

Recently Ferraro [7] said that plaques in the cerebellum were derived from Purkinje cells, and maintained that the smaller plaques were formed from the micro- or oligodendroglia cells, and the nerve-cells.

Simchowicz [16], however, believes that the process begins with an atrophy of the finest nerve elements; this was formerly looked upon as a possible explanation, though it could not be proved by the available technique. This atrophy is probably followed by a thickening of the neuroglial reticulum, the meshes of the network become smaller, and when at a later stage the products of metabolism are deposited in this thickened network some of the neuroglial cells set to work to remove them. He believed that the axis-cylinders at the periphery of the plaques undergo partly degenerative, partly regenerative changes; the glia in the neighborhood reacts by the formation of large cells, the fibres of which form a capsule round the plaque. In 1924, Simchowicz [17] corroborated what he had said in his first publication. Perusini [15] was the first to speak of a thickening of the glial reticulum. On the other hand Fischer [8] was unable to find anywhere a close connection between the plaques and the glia.

Without wishing to quote too much from the extensive literature on the subject, I must mention Marinesco's [13] opinion. He said that the first stage was characterized by the deposition of a substance in the brain-tissue which came from the circulating interstitial plasma; the colloidal equilibrium of the plasma is disturbed either by a too large accumulation of this substance, or by another unknown cause. The substances are deposited electively, especially in the cortex, beginning as small isolated threads which later grow by apposition of new elements of the same kind (p. 106). The second phase of the process is characterized by a reaction on the part of the nerve-fibres. At first only a limited number of fibres react, in many cases only one which develops a clear large swelling. After the plaque has developed, this swelling forms the central nucleus, or rather that portion of the central part of the nucleus which is left after the inclusions have been dissolved, and which is stained by anilin or hæmatoxylin dyes (p. 127). The nerve-fibres in the senile plaques show regenerative phenomena; this is the stage of reactive changes; soon afterwards we get the degeneration of nerve elements (p. 127). The third stage is characterized by a progressive deposition of substances in the plaque and by a penetration of new fibres and cells into this, which leads to a gradual increase in size of the plaque, so that gradually large areas of the cortex of the brain may be implicated, unless another factor intervenes which prevents the senile plaques increasing in size; this factor is the neuroglial reaction.

The neuroglia plays its classic part as "Füllungsgewebe," but it seems to have another important function, viz., that of eliminating the stringy inclusions, beginning at the periphery and progressing towards the centre. It would seem as if the neuroglia worked as a secretory organ capable of dissolving the deposits (p. 128). As far as I have been able to find out Löwenberg [12] was the first to speak of disintegrated astrocytes forming a plaque, although he too admitted that the latter might be formed from various elements of the central nervous system, especially from the glial reticulum. If many astrocytes disintegrate at the same time, a large plaque is formed. The astrocytes are heaped up round the vessels and this is followed by a progressive disintegration of the cells and structures, producing all the features of a senile plaque. Its formation is thus dependent on an alteration of the vessels. After the Hortega method came into general use the Hortega cells were looked upon as important elements in the formation of plaques. Timmer [20] believes that the nucleus of the plaque is formed by a rounded or disintegrated Hortega cell which takes up the products of metabolism and tries to digest them in the normal way, but being weakened by senility it is unable to do so and disintegrates. Other Hortega cells are attracted by the nucleus of the plaque and begin to break it down. The outer ring is formed by a network of microglial dendrites. The processes of the Hortega cells, which are radially arranged in the plaques, become thick on the side of the cell furthest away from the nucleus of the plaque, as a reaction to the chemiotactic influences. The fine network of thickly plaited filaments which they make constitutes the outer ring of the plaque. The macroglial cells form a capsule round it. In the meantime the Hortega cells deal with the noxious substances which have been deposited, and when they disintegrate the plaque disappears.

According to Urechia and Elekes [21] Hortega's method reveals more plaques than the Bielschowsky staining, and one can see that the oligodendroglia and microglia take an active part in the formation of the plaques. Altered oligodendroglia cells may, together with a Hortega cell, form a dwarf plaque. In the classical larger plaques the centre usually consists of degenerated oligodendroglial cells, some of these having been melted into one mass, and to lesser degree by degenerated Hortega cells. In more advanced stages the central mass disappears, and the plaque then only consists of more or less altered Hortega cells and the protoplasmic "processes" of the "apolar" cells. The plaques may finally disappear; first the nuclei, and later the fibres, grow paler and undergo a granular disintegration.

In my cases I find microglia as well as macroglia, and occasionally oligodendroglia, round the plaques. The microglia especially seems to take an active part in their formation, and has been the object of much study in this connection since the investigations of Hortega. When we see a plaque surrounded by microglial and macroglial cells we must look on these cells as troops mobilized round a threatened place (fig. 2). One gets the impression that the microglia here is not only swollen, but also that the cells have absorbed abnormal products. We sometimes see multiple branchings ending in bulblike swellings, and appearances which look like amitotic nuclear divisions. Microglia also penetrates into the plaques, and there is an increase in the number of cells round both the diffuse and the felted plaques.

The microglial cells within a plaque are stained darkly (fig. 1), and the bodies of those in the neighbourhood of the plaque are swollen and darker in tint on the side nearest to the plaque. This may be interpreted as a pathological alteration of the microglia, the disintegration of which will lead to the formation of the granular amorphous substance from which the argyrophile mass of the plaque is derived.

Whereas many look upon amyloid as the chief substance formed, Hechst [11] maintains that plaques coloured by Scharlach R and Sudan III often take on a pale red tint. He found that staining with Turnbull's method for iron showed that the Hortega cells lying radially in the plaques were either diffusely permeated with iron, or their bodies and dendrites contained fine iron granules, particularly the dendrites nearest to the centre of the plaques.

We must be cautious before deciding that the microglia cells in the centres of the plaques have been subject to alterations; the end of a blood-vessel cut longitudinally may simulate a microglia cell.

Pale and indefinite plaques are surrounded by oligodendroglial cells (fig. 2). I believe, contrary to some authors, that these particular cells do not often play an active part in its formation. Hortega takes the same view.

Opinion is divided as to the part macroglial cells take in the process. Ferraro says that there are sometimes astrocytes in a more or less advanced stage of degeneration in the middle of the plaque. Löwenberg believes that it is possible that a disintegrated astrocyte may be the beginning of a plaque. It cannot be denied that some details in successful Holzer preparations suggest that this is so. Clasmato-dendrosis may be found in such preparations. Figs. 3 and 4 show this, and also the necrosis of vessels, which have been broken up into

fragments. Many vessels were present in this section just as in Löwenberg's preparations. There are, however, obvious differences between the thick fibrils of the astrocytes, and the thinner ones of the plaques. The first are sometimes found in large numbers round the plaques, where they can easily be recognized, especially in the hippocampus. Some of their fibres may help to form the outer ring. The numbers obtained by counting these fibres vary much in the Bielschowsky, Hortega and Holzer preparations, although these various preparations have been taken from successive sections of one block.

Struwe [19] says that plaques cannot develop from ganglion cells, Hortega cells, astrocytes and oligodendroglial cells. They originate independently of affections of vessel walls but in rare cases they lie on the vessel wall. "Fädchenherde" and "Filzwerk" are similar to senile plaques, but the tissue found in them is less altered than in a senile plaque.

It is often assumed that the formation of a plaque is dependent on disease of the vessels, or that it is connected in some way or other with the vessels. If this is so then arteriosclerotic disease of the vessels would prove to be one of the chief factors in plaque formation. But we are often unable to find either plaques or "Filzwerke" in dementia arteriosclerotica, while in most cases of simple dementia senilis with plaques no definite disease is present in the vessels.

In the brains of some patients who had suffered from senile dementia, however, I was able to find a large number of sections that demonstrated beyond doubt the perivascular genesis of senile plaques. In 1924 [4] I published the first of these cases. Against the wall of small blood-vessels in the cerebral cortex a small territory is first seen to be filled up with, or changed into, a colloidal mass. This mass enlarges, it soon shows a radial striation in its periphery, and then protuberances grow out of it in rows, the peripheral parts of which afterwards anastomose. In this way the central nucleus with its radial striation, the open area and the wreath are produced. In most of these senile plaques the small vessel in the centre disappears (figs. 5, 6, 7). In my opinion, however, plaques of perivascular origin are infrequent: senile plaques usually develop independently of the vessels.

Divry [6] pointed out that we know little or nothing of the chemical nature of the plaques. After some histochemical experiments he came to the conclusion that the nuclear area consists of amyloid substances and the outer zone of a hyaloid substance which formed the matrix of the amyloid nucleus; the plaques therefore represent a disseminated

and miliary hyalino-amyloidosis. These experiments with iodine-Congo-red were repeated by Prof. Ringer, at my request, with the same result. It is remarkable that Hechst too, who has dealt fully with the histochemistry of the senile plaques, believed that the nucleus and the outer ring consisted of amyloid substances. In his beautiful drawing of a Congo-red preparation of a senile plaque we see that the nucleus and to a lesser extent the wreath have taken on the red colour. Amyloid is not always deposited in the form of plaques in the central nervous system. Amyloidosis is, however, an independent circumscribed process in the central nervous system, and no part of a general amyloidosis. The amyloid of the senile plaques can only originate in the parenchyma of the central nervous system, either from the disintegration of the nerve-cells, or from the necrobiosis of the neuroglia; the first possibility seems the most probable. Amyloid is most probably a disintegration product of the pathological metabolism of nerve-cells, and the primary factor in the plaque formation is the precipitation of amyloid from solution in a crystalline form, usually round the vessels.

Ferraro has also studied the histochemistry as well as the histopathology of this subject. He says that it is at present unknown what really happens histo-chemically when a cell element is transformed into a senile plaque. We can only say that a granular argyrophil substance is formed, which in the central part of the plaque sometimes gives some of the amyloid reactions, and at other times the reactions of fat.

Struwe too believes that the plaques originate from the crystallization or precipitation of products of metabolism. Besides the hyaloid and amyloid substances of Divry, he found that the nucleus often contained lipid substances. He believed that the nature of the glial reaction could be used as a measure of the duration of the process. Plaques where the Hortega cells are beginning to increase are not coloured by fat stains. We find in them at first a clear yellow lipid which has much the same colour as the nucleus, but later red-coloured fat is present. At this stage the Hortega cells become gradually rounded off into fat globules and the astrocytes begin to increase (p. 296).

Further knowledge is necessary before we can form a correct judgment about the pathological processes in which metabolism and chemical processes certainly take part.

The torpedoes—As to the torpedoes, the "Axonschwellungen" of the Purkinje cells, I can refer to my article of 1928 [5]. In all the brains studied microscopically, from patients who had suffered from senile dementia and in which I found senile plaques, I was able to find these

torpedoes. In preparations in which the nerve-fibres are impregnated (e.g. in Bielschowsky silver impregnation) they are visible as large spool-like thickenings of the neurites in the cerebellar cortex; in most cases they lie in the superficial zone of the granular layer at a relatively small distance from the Purkinje cells. They are of nearly the same size as these Purkinje cells and twice or thrice as long as broad. Both ends of the spool gradually pass into a normally impregnated neurite. In many instances it can be seen that this neurite comes from a Purkinje cell. As a rule the torpedoes are impregnated fairly homogeneously and somewhat less intensely than the neurite itself, but more deeply than the body of the Purkinje cell. In a number of the torpedoes small vacuoles can be found. As far as I can see these torpedoes are identical with the local swellings of neurites found by Cajal in injuries of the cerebellar cortex. Cajal took them to be analogous to the varicose swellings that appear in the neurites of other parts of the nervous system after they are severed. In senile dementia however no severing of the neurites of Purkinje cells has yet been found.

Torpedoes occur in other diseases, as in amaurotic idiocy, general paralysis, tuberculous meningitis, &c. I have found them in all my cases of senile dementia.

The Alzheimer type of fibrillary alteration.—The Alzheimer type of fibrillary alteration [1] is also constant in senile dementia. I have always been able to find cells in the cerebral cortex showing this change in my cases of senile dementia. In some of the brains however I had to look carefully for them.

Opinions about Alzheimer's fibrillary alteration differ considerably. It is generally known that in ganglion cells subject to this change thick bundles of parallel neurofibrils are seen which are impregnated more easily than normal and take a deep black shade. The bundles are usually curled, producing an appearance like coils of hair. Simchowicz looks upon them as the effect of an extracellular lesion. The neurofibrils in the large motor cells of reptiles alter during their winter sleep, forming rough isolated thick bundles (Cajal, Tello). When the animal is warmed the fine fibrillar net reappears with the manifestations of motor life. In mammals alterations of the fibrils take place under the influence of changes of temperature, periods of famine and poisons. In such cases we do not speak of hyperdifferentiation but of a fusion. The fibrils may also show alterations under the influence of certain infections. Marinesco and Minea describe a thickening of the fibrils in the spinal ganglion cells, comparable to Alzheimer's fibrillary alteration, in rabies. They spoke of a fibrillary hypertrophy.

Alzheimer will not accept the term fibrillary overgrowth, used by Fischer. Bielschowsky [2] believes that in Alzheimer's disease a new substance, foreign to the cell, has been deposited, causing the new coil-like form. He doubts if this process is the same as the fibrillary alterations described above. The view that in rabies, &c., we have to deal with an hypertrophy of the fibrils is not shared by Spielmeyer [18], who speaks of an "Umwandlung" of the fibrils, which have become impregnated with some substance. My opinion that Alzheimer's fibrillary alteration is a constant phenomenon in senile dementia is partly shared by Simchowicz and by Grünthal [10] who was unable to find the Alzheimer fibrils in two cases only of senile dementia.

Many workers have tried to find out whether the occurrence of plaques had any regional preference, as is the case with Alzheimer's fibrillary alteration. Marinesco and Minea found the regional distribution of the older plaques to be the same as that of the Alzheimer fibrils, i.e. in the cornu ammonis and subiculum. In brains in which there have been few Alzheimer's fibrillary alterations, I have also found only simple or early senile plaques. The early stage of Alzheimer's fibrillary alteration occurs where lipoid is present, and in most of the cells this is at a spot between the nucleus and the origin of the neurite, corresponding to the fibrillogenic zone of Held, where the first fibrils develop in the young neuroblast. Spielmeyer has found this also in his series of Alzheimer's fibrillary disease. In Spielmeyer's examples there were argyrophil fibrils in the dendrites, but even these were not present in my cases, where the process was only beginning. Alzheimer also illustrates these argyrophil fibres in the dendrites (fig. 7 of his publication). He says that the alterations usually begin in cells in which there is ordinarily a large amount of fat. Marinesco and Minea [13] also have reported that the thickening usually commences where pigment is present (p. 122).

Eyes, buds, knots, &c., in the neurites, passing through senile plaques.—In the centre of all the well-developed plaques the neurites have disappeared. Many of the surrounding neurites pass tangentially to the surface of the plaque, making leashes of parallel fibres around it as if they were pushed away by its outgrowth. Others, however, enter the plaque and end abruptly in its superficial layers as if they were cut. In some plaques the entering neurites do not end abruptly, but present exactly the same differentiations as are seen after section of a fibre, i.e. a tendency to stain deeply, small end-buds, varicose swellings, knots and eyes and even "Entbündelungserscheinungen" (figs. 9 and 10), a term

used by Heidenhain for the following appearance: "The fine thread-like fibrils passing from the dendrites into the cell bodies become broader, forming bands with clear parallel stripes on them, in the neighbourhood of the cell nucleus. At a shorter or longer distance from this they are again united into a solid thread." Bielschowsky (p. 69, fig. 40) describes "Entbündelungserscheinungen" in the axis-cylinders inside a Meissner's body.

Finally, there are formations similar to those found by Perez [14] in the skin of the pulp of the finger [sub-basal plexus and intersudoral ivy-like end branches]. In fig. 9 there is a strange formation which when photographed on a deeper plane looks like a torpedo. In fig. 8 there is a curious mixing up of elements; I suggest calling this condition an "actinomyces-like plaque." It is possible that a cell undergoing Alzheimer's fibrillary alteration together with a torpedo-like formation forms the centre of the plaque (fig. 12). Argrophil fibres and fibres with buds and eyes may also be found in the plaque itself, especially in the outer ring and interspersed throughout the diffuse plaques (figs. 9 and 10). Naturally the question arises whether all these formations, as the torpedoes, are evidences of degeneration or regeneration, a question which Bielschowsky has discussed. He thinks it is impossible to regard them as degenerative processes. He believes that although degeneration may cause longitudinal splitting of fibres and consequently the appearances of branching, the length of the terminal fibres and their frequently winding and recurved course is against such an interpretation. There is certainly no over-production of regenerative nerve shoots such as is not seldom met with in the neighbourhood of other lesions. There is never more than an indication of this process, and the newly formed material seems to have only a short life.

I actually rediscovered the occurrence of all these knots, eyes, &c., in senile plaques at a time when I did not know that Fischer [8] had made drawings of them (*see* figs. 25-35). He says that the longer axis cylinders often show spool-like swellings in the neighbourhood of the plaques, sometimes only vaguely indicated, sometimes much more marked. Probably Fischer generalized too much when he spoke of the wreath-like formation round the plaque as being formed of axis-cylinders with their thin parts pointing inwards and their knotty ends outwards. With newer methods of staining it is evident that in many instances they are not axis-cylinders but microglial cells.

Fischer speaks of the spool-like swellings and of the splitting of the axis cylinders; the latter is identical with "Entbündelungserscheinungen"

(fig. 10). He saw knots on the swollen axis cylinders, and found the thick argyrophil axis cylinders passing through the plaque although the majority were unstained.

Marinesco and Minea have described as reactive phenomena of the fibres hypertrophic fibrillation, the formation of fine collaterals, and small, thick and short buds, either homogeneous or fibrillary in structure, and delicate branchings which soon end in small homogeneous knots, or divide to form two or several such formations. The finest collaterals often end in small rings. A few fibres running an unbroken course may by their collateral branches form a series of terminal formations, the number of which corresponds with the number of fibres involved. Marinesco and Minea refer to the regeneration of peripheral nerves as a reaction to the interruption or section of the fibres and compare this with what has just been described. The alterations in the nerve-fibres show that the substance deposited in the plaques has no local toxic influence, for if it were so there would be regressive changes in the fibres. On the contrary there is an attempt at regeneration which, however, does not progress beyond the first phase. Mechanical obstacles or the lack of a positive chemiotactic influence may be the reason why the reactive regeneration stops at this stage; the specific elements then develop further in an exaggerated, abnormal or even monstrous way, and finally degenerate. The nerve-fibre may then produce a second series of end-swelling, so that a whole series of pathological formations may in this way develop from one single fibre.

Simchowicz mentions buds or eyes at the free ends of the fibres. He speaks of the division of the axis cylinders and says that the newly formed shoots form buds at their ends, so that sometimes numerous shoots are found, giving the picture of a tree with many branches. He looks upon it as a form of regeneration.

It is necessary to refer to torpedoes in discussing the question whether we have to do with regeneration or degeneration. No obstacles or breaks in continuity which would explain a regeneration were observed; though there was a reaction, it was not vigorous enough to lead to the formation of new elements or collaterals. In certain diseases the term regeneration may be used, but what is generally found in dementia senilis does not warrant our employing the term here. The same applies to the alterations in the nerve-fibrils described above.

It is an important observation that plaques are never found in parts where there is much atrophy of the brain, nor are torpedoes,

Alzheimer's fibrillary alteration, or branching or "Entbündelungserscheinungen" of the neurofibrils. Struwe too noticed that in severely atrophic parts of the brain no conglomerations of glial fibres or plaques were found. He attributes this to the altered conditions of circulation and nourishment, as in general paralysis, in which disease iron in the cells of the vessel wall and in the Hortega cells is altogether absent in parts where there is severe atrophy.

The characteristics, common to the four groups of alterations, found in senile dementia.—The four groups of alterations typical of senile dementia having now been described we can discuss the characteristics common to all in order to get an idea as to their common cause.

The simplest changes are the small eyes, knots and buds that occur in some of the neurites in senile plaques. As far as microscopical study reveals it, their structure is identical with the changes which are found after a living nerve has been cut. The regeneration of severed neurites begins with the formation of similar knots, buds and eyes in these neurites at the central side of the lesion. This central part of the neurite is continuous with the body of its ganglion cell, and out of this central part the new neurite will develop. It is known that at the beginning of this regeneration the process of differentiation seems to be greater than is necessary for the formation of the new neurite; a number of fine neurites often grow out from one old fibre, and numerous swellings and side branches develop which afterwards disappear. It seems that the differentiation that will replace the lost structures is at first too rich, overpassing the limits of the normal, but that afterwards these temporary "overdifferentiations" regress until the normal is attained. This mechanism, which can be designated by the name "hyperdifferentiation," is not limited to the nervous system. It is common in nature when a damaged organism tries to rebuild the lost parts. The excessive outgrowth of a severed nerve-fibre may be compared with the formation of callus in a broken bone.

Now in some of the senile plaques precisely the same peculiarities are met as we find in the well-known hyperdifferentiation which occurs in regeneration after damage: we see the typical neuritic swellings, knots, buds, eyes, "Entbündelungserscheinung" and neurites with increased argyrophilia, &c. A lesion severing fibres has not been demonstrated in senile dementia, but the absence, or the small number, of neurites within the senile plaque indicates that some have been lost. It is possible, however, that these neurites are not really destroyed, but simply pushed aside by the plaque. So although we do not know with

certainty that the neurites are damaged, we can state that this first group of alterations has morphological features identical with those occurring in hyperdifferentiation.

The second group of alterations found in senile dementia are the torpedoes in the cerebellum. They are identical with other changes in hyperdifferentiation, as the neuritic swellings found by Cajal after cutting the living cerebellar cortex, and the swellings in the course of a neurite after it has been divided. It is not certain that the neurites of the Purkinje cells were damaged, and consequently we do not know if the torpedoes in senile dementia are reactions of the living neurite to lesions. These alterations in senile dementia are, however, identical with certain features of hyperdifferentiation.

A number of authors have expressed the opinion that Alzheimer's type of fibrillary alteration can be caused by damage of the neurite, that it is a special form of reaction to such damage. This is possible, but this type of alteration suggests an exaggeration of the normal structure. In a ganglion cell affected by it the intracellular neurofibrils impregnate more readily, and are more numerous than normal. They resemble the "Entbündelung" that arises in regenerating nerves.

Consequently, a characteristic common to these three groups of alterations in senile dementia is their close resemblance to the effects of what I have called hyperdifferentiation, which is seen in the early stages of the regeneration of nerve-fibres.

Is it possible perhaps to regard the senile plaque as a result of hyperdifferentiation? It is difficult to believe that the amorphous argyrophil masses of the senile plaque should result from hyperdifferentiation of a neurite or a ganglion cell. No changes in neurites or ganglion cells are known that resemble these amorphous masses, or that would account for the irregular network which is built up in a senile plaque by them. If the plaque were a form of hyperdifferentiation, we should have to consider the possibility that it was a hyperdifferentiation in the ground tissue of the central nervous system, that is in the glial reticulum. It is highly probable that in normal development the neurites develop within the protoplasm of this reticulum, perhaps the neurofibrils themselves are a differentiation of it.

From a physico-chemical point of view the idea of neural hyperdifferentiation of the ground reticulum is applicable to the plaques; these react to silver impregnation, in the methods of Bielschowsky or of Cajal, exactly as the neurofibrils. The occurrence of argyrophil masses in the plaques therefore means that there had been a physico-chemical

alteration of the ground tissue in the same direction as that which characterizes the neurites.

On the other hand the morphology of the plaque is highly different from that of a neuron; its structural differentiation is so primitive that one might speak of amorphous masses. The argyrophil clumps of a senile plaque might be regarded as the result of an attempt on the part of the ground tissue at neural differentiation; an attempt which has more or less succeeded from a physico-chemical point of view, but not from the morphological side. This may be explained by the fact that the ground reticulum is normally less differentiated than the neurites and the ganglion cells, and consequently hyperdifferentiation cannot reach such a high degree in it.

The four histological alterations which occur in senile dementia can therefore be brought under a single formula: "hyperdifferentiation," that is an attempt of the nervous tissues to differentiate in the direction of a specific neuron, an attempt which may advance beyond the normal. If this hyperdifferentiation occurs in a ganglion cell the Alzheimer type of fibrillary alteration results; if it occurs in the course of a neurite a torpedo is formed; if it occurs in dendrites dendritic swellings develop; if it occurs in the neurites that are involved in a senile plaque the eyes, buds, knots, "Entbündelungserscheinungen" and argyrophile fibres result; and if it occurs in the non-differentiated protoplasmatic ground reticulum of the nervous system a senile plaque is born.

We do not know what irritating agent it is which leads to this hyperdifferentiation, and to the formation of the plaques. It is possible that it is a reaction to trauma of the tissues, a disproportionate attempt of the nervous tissue to regenerate after a primary lesion. The fact that most of the neurites in a senile plaque have been destroyed would be accounted for by such an hypothesis. And the views of the many authors whom we have cited above, that a primary degeneration of nervous tissue is the first stage of the genesis of the senile plaque, is in accordance with such a possibility. There is however no certainty about this and our knowledge of the genesis of these senile structures is not clear.

Still I believe that by the hypothesis which I have put forward all the peculiarities of this disease can be considered from one and the same point of view, and that it will help us to understand the nature of the process which has resulted in the development of senile plaques.

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LEGENDS OF ILLUSTRATIONS.

PLATE V.

- FIG. 1.—Microglia cell in a senile plaque.
- FIG. 2.—A plaque surrounded by different types of glial cells.
- FIG. 3.—Glial fibrils around the plaque.
- FIG. 4.—Glial fibres and swollen macroglia cell around the plaque.
- FIG. 5.—Senile plaque around a blood-vessel. Early form.
- FIG. 6.—Senile plaque around a vessel. Later stage.

PLATE VI.

- FIG. 7.—Senile perivascular plaque. Full grown form.
- FIG. 8.—Actinomyces-like plaque.
- FIG. 9.—Different alterations of the neurites in the outer ring of a plaque.
- FIG. 10.—Different alterations of the neurites in the periphery of the plaque (a.o. "Entbündelungserscheinungen").
- FIG. 11.—Torpedoes in a plaque.
- FIG. 12.—Alzheimer fibrillary alteration in the centre of a plaque.

PLATE V.

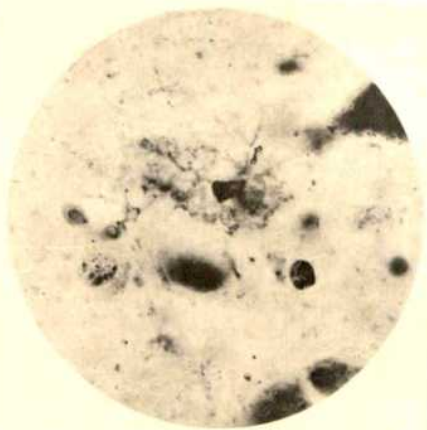


FIG. 1.

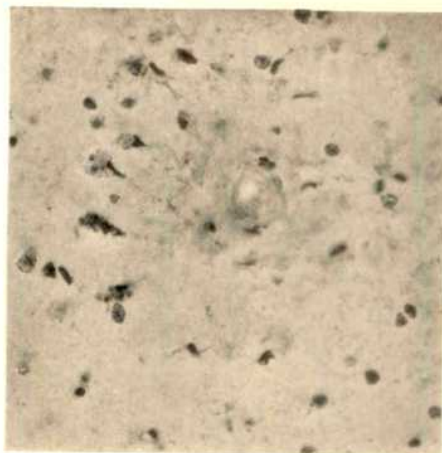


FIG. 2.



FIG. 3.



FIG. 4.

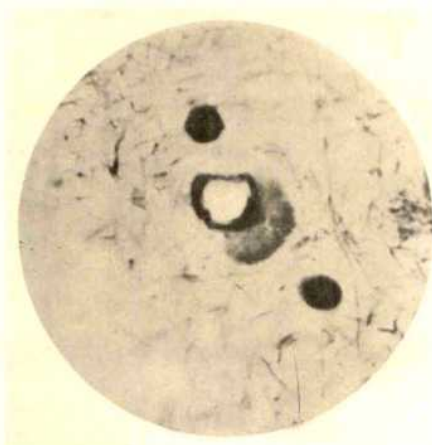


FIG. 5.



FIG. 6.

PLATE VI.



FIG. 7.

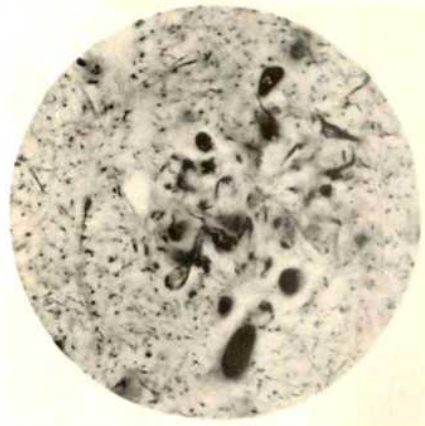


FIG. 8.

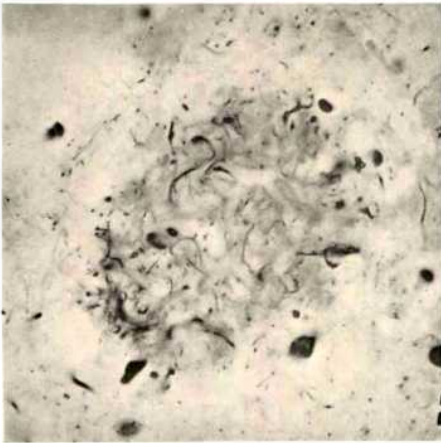


FIG. 9.

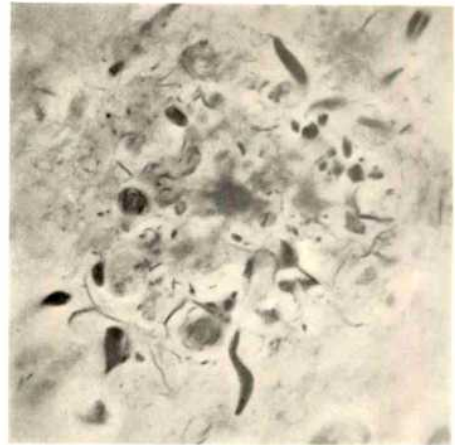


FIG. 10.

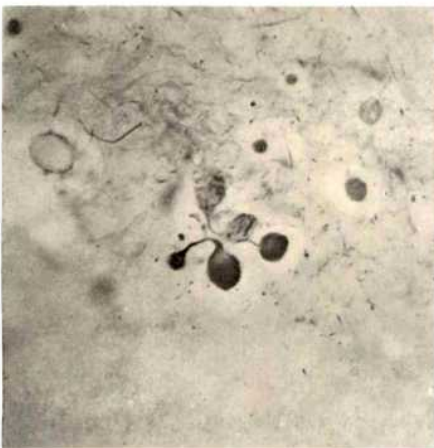


FIG. 11.

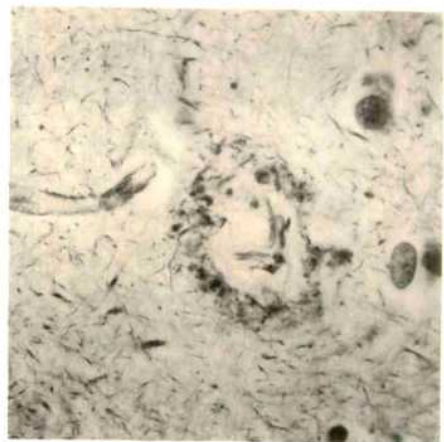


FIG. 12.

To illustrate paper by L. Bouman.

THE INTRINSIC NERVOUS MECHANISM OF THE HUMAN LUNG.

BY JOHN B. GAYLOR.

(*From the Institute of Physiology, the University, Glasgow.*)

MUCH has been written about the morphology and physiology of the lungs, and agreement has been reached on many of the fundamental points of respiratory function, but in the intrinsic innervation of the lungs there still remains a field of investigation where much is not clear and where much that is known has been left unexplained. The motive of the following inquiry has been to investigate histologically the innervation of the human lung, bearing in mind the findings of physiological and clinical science.

Historical survey.—The first piece of work dealing with the innervation of the lung is that by Rémak (1844). He described a careful dissection of the lung of the ox and was able to reveal strands of tissue beset with nodal swellings in the bronchial adventitia. Rémak recognized these structures as nerves and ganglia, but as his technique was limited to the methods of dissection he was unable to display any of the finer ramifications of nerve-fibres. Arnold (1863), in a general histological study of the lung, recognized the same structures as did Rémak. He had no idea of the ultimate nature of the nodosities on the course of the peribronchial nerves, but observed a certain similarity between them and the nodosities which exist on the sympathetic chain. By the use of acetic acid he was able to make out small bodies inside the nodosities: these he terms "Glockenkörper"; they appear to be actual ganglion cells. An advance came with the application of Ranvier's chloride of gold method to the lung. Ismajloff (1873), using this technique, described three different plexuses at specific levels in the thickness of the bronchial wall. In addition, he stated definitely the origin of the lung nerves to be vagal and sympathetic through the pulmonary plexuses. Stirling (1882), working on the lung of the newt and using chloride of gold and osmic acid technique, made the observation that medullated fibres do not run continuously in a single trunk in the plexus, but from strand to strand. He proceeded to a description of a primary wide-meshed plexus giving rise to, and containing in its meshes in the same

plane, a secondary finely meshed plexus. Stirling demonstrated nuclei at the nodes of the primary plexus and made the observation that the nuclei had nothing to do with the medullated fibres. He was undoubtedly seeing nuclei of ganglion cells; one can, in the light of present knowledge, appreciate Stirling's statement. It is well known that many medullated fibres pass directly through the ganglia of the lung without interruption, but greater technical facility would have shown Stirling that certain medullated fibres lose their medullated sheath just before entering the ganglion—an observation in consonance with the modern concept of pre- and post-ganglionic fibres.

A passing reference must be made to the work of Simanowsky (1888), who, in an investigation into the nature of the mucosa of the larynx, described intra-epithelial endings. The description of nerve-endings, and in particular intra-epithelial endings, is a distinct advance which later workers extended to the lower reaches of the respiratory tract. Retzius (1894) was enabled to show, by technique superior to any hitherto used, nerve-endings in the mucosa of the larynx over the transition between the stratified squamous and ciliated columnar epithelium as it exists in the larynx. He showed that there was no fundamental difference in the mode of sensory innervation of the two epithelia as far as the microscopic appearances went. By the use of other technique, Fusari (1894) was able to confirm the work of Retzius. Berkeley (1894), employing one of the earliest methods of specific silver impregnation, described a peribronchial plexus and a subepithelial plexus in the larger bronchi. With diminution in the calibre of the bronchi the differentiation into two plexuses became less distinct until, in the smaller bronchi, only one plexus could be seen. He demonstrated further that the two plexuses in the larger bronchi were not independent the one from the other, but that there were numerous connections between them. Berkeley also described intra-epithelial endings, on the origins of which are heavily impregnated varicosities; these he suggested erroneously to be ganglia. Fine branches were found to arise from the outer bronchial plexus to ramify in the plain muscle layer; the endings of these fine branches were described as small varicosities between the plain muscle cells. The remarkable work of Berkeley not only established the authenticity of intra-epithelial endings, but directed attention to the demonstration of the motor innervation of the smooth muscle of the bronchial tree. His description of alveolar endings, the existence of which was a matter of doubt, has been recently observed in the human lung (Larsell and Dow, 1933).

Arnstein (1897), apparently stimulated by the work of Retzius, set himself the problem of investigating the finer morphological points to be made out in the ganglia and nerve-endings of the respiratory tract. Although his main interest lay in the innervation of the trachea, larynx and epiglottis, it is worthy of note that he was able to stain nerve-fibres in dissociated columnar epithelial cells. He showed such a cell in isolation with a fine varicose nerve clinging to the cell membrane. Of some importance is his observation of the difference between the innervation of the epithelial membrane of the upper respiratory tract and the lower. In the epiglottis and upper larynx there are endings free in the sub-epithelial tissue; these endings are mainly end-bulbs. No such endings are demonstrable in the trachea, and certainly no subsequent worker has been able to show them in the bronchi. The natural conclusion to be drawn is that more forms of sensation are received from the upper part of the respiratory tree. The ganglia of the trachea and of the bronchi have so much in common that some mention must be made of Arnstein's work in this direction. According to his observations large medullated fibres pass directly through the ganglia, fine medullated fibres end in the ganglia, and non-medullated originate there. One may be justified in making the conclusion that the first are sensory fibres of parasympathetic origin, the second pre-ganglionic fibres, and the third post-ganglionic fibres. Wolff (1902) reminds us of the work of Berkeley in describing intra-epithelial endings and interalveolar endings. The latter are extremely doubtful.

In the work of Dogiel (1903) we find the first extensive attempt to investigate the morphology of the pleural innervation. He found the parietal pleura to be richly innervated. Vater-Paccini corpuscles as well as free endings under the endothelium in the neighbourhood of the fat cells are described. No such structures are seen in the visceral pleura, although McLaughlin (1933) suggests that the visceral pleura has a rich innervation from his histological studies. It must be admitted that the view which sets forth the visceral pleura as being poorly innervated and the parietal as being richly innervated, is much more in accordance with the facts of experimental physiology. The careful observations of Capps (1911) on patients who were submitted to paracentesis of the chest show quite clearly that the visceral pleura is insensitive to pain. Should a patient complain of pain when the visceral pleura is stimulated the phenomena can be explained always by adhesions causing traction on the parietal pleura. It is noteworthy that Capps showed that pain can be localized in the parietal pleura and that the sensation

is mediated by the intercostal nerves. The diaphragmatic pleura has its sensory innervation from two sources; the peripheral part from the intercostals and the central part from the phrenic. Pain in the segmental skin distribution of nerves from the phrenic spinal segments is experienced when the central part of the diaphragmatic pleura is stimulated.

Ponzio (1906) investigated the innervation of foetal lungs and of the lungs of the newborn. He used the methylene-blue technique. His observations extended beyond those which were confirmatory of previous work on the existence of a plexus originating in the small bronchi and ramifying through the entire interalveolar septa. He described a plexus existing on the walls of the capillaries of the lung. The observations of Ponzio cannot be accepted, and I am not alone in a refutation of them. Stöhr in a review of the literature (*Handbuch der mikroskopischen Anatomie des Menschen*) doubts the validity of Ponzio's work. Larsell (1921) has, from his experience of the methylene-blue technique, expressed the opinion that the structures which Ponzio illustrated are the result of non-specific staining. During the earlier stages of my own work I was able to produce pictures similar to Ponzio's, but I was convinced by using other staining methods as controls that the gross interalveolar plexus was composed of elastic tissue, that the plexus round the capillaries was a meshwork of intercellular cement substance in the endothelium, and that the results obtained were due to imperfect technique. Larsell (1921, 1922-23) made a very thorough investigation of the pulmonary innervation in rabbits. He used a specially modified methylene-blue technique and was able to obtain a constancy of results which show remarkable differential nervous staining. He proceeded in later work to combine this technique with experimental section of the vagus, and noted the subsequent effect on the nerve-endings which he had hitherto demonstrated. The general conclusions of Larsell are that there exist an extrachondrial plexus rich in ganglion cells and myelinated fibres and a subchondrial plexus poor in ganglion cells and composed mainly of non-medullated fibres. The ganglion cells are provided with pericellular basket-works, the terminal arborizations of pre-ganglionic fibres which are medullated. He states that the post-ganglionic fibres go to the smooth muscle of the bronchi to afford a motor supply and also go to the bronchial mucous glands. In connection with the richness of the pre-ganglionic fibres which innervate the lung, Larsell made the interesting observation that the vagus is much poorer in medullated fibres, both relatively and absolutely, after the

lungs have been supplied. There is another reason for this fact in that the afferent impulses from the lung travel through the vagus and are carried by medullated fibres. A very important contribution was made to the study of lung innervation when Larsell described "plain-muscle spindles." These branching endings arise from large medullated fibres of vagal origin, and are found in the smooth muscle of the bronchi. There can be no doubt that they are sensory in function. Although Stöhr questions the existence of such structures, he had only the observations of Larsell and Carpenter (1918) on which he might base his opinion when he wrote his review. Carpenter demonstrated sensory endings in the smooth muscle of the intestine by the use of methylene-blue technique. These endings present certain morphological differences from those of the lung, and this is possibly the reason why Stöhr finds difficulty in admitting the "smooth muscle spindle."

Jones (1925-26) working with reptilian lung and modifying the Larsell technique to suit his material, demonstrated precisely the same type of ending in the smooth muscle of the bronchi. This further demonstration might still leave the issue in doubt since the objection may be raised that the structure has been demonstrated by methylene-blue technique only. There is also the objection that the structure demonstrated in the gut differs from that in the bronchi. Sunder-Plassmann (1933, *a*), by the use of silver, showed a type of ending in the carotid sinus. This ending, and that which I demonstrated to the Association of Physicians of Great Britain in April, 1933, are exactly similar. My demonstration of such a "smooth muscle spindle" in the lung has been shown also by Sunder-Plassmann (1933, *b*) in the same situation. Whereas the endings which Sunder-Plassmann and I have stained by silver differ in appearance from those which have been shown by methylene blue, it is likely that the morphological basis is the same and that the differences in appearances are accounted for by differences in reaction to the technique employed. All these endings arise from coarse medullated nerve; they appear to have the same relationship to the plain muscle cells; all are branched. Larsell and Dow (1933) have extended the previous work of 1921 and 1923 to the study of the innervation of the human lung. The results of their investigations show no fundamental difference between the microscopic picture of rabbit lung and human lung innervation.

We must examine briefly the work which has been done to elucidate the central connections of the pulmonary nerves. The method of approach has been through the study of degenerative changes subse-

quent to nerve section or to lung extirpation. As these investigations are incidental and are not concerned with the main theme of this work, I shall be content to cite the more important conclusions on which agreement has been reached. It is important to be conversant with our present knowledge of this matter in order that we may understand the significance of the intrinsic pulmonary innervation. Müller (1911) in a survey of the anatomy, histology and physiology of the vagus nerve, gave an account of the afferent impulses from the lung. He argued that the humoral influences in respiratory control are subservient, under certain conditions, to the afferent impulses from the lungs. An example of such inhibition of normal respiration is the stimulation of the bronchial mucosa by some irritant producing coughing.

Möllgaard (1912) investigated the central distribution of the pulmonary fibres of the vagus. This work is classical and the more important conclusions which he made have not been questioned. Of note is the confirmatory work of Iwama (1925, *a* and *b*) and Molhant (1913). Möllgaard observed the presence or absence of degenerative change in the cells of the cervical ganglia, the ganglion nodosum, and the dorsal nucleus of the vagus, along with carefully controlled observation of the vagus trunk itself, after extirpation of a lung in whole or in part. The general conclusions of Möllgaard are that, although the dorsal nucleus of the vagus has to do with pulmonary innervation, no axis cylinders travel directly from their cells of origin in the central nervous system to an ultimate distribution in the lung. The ganglion nodosum contains cells which are the exact analogues of the cells of the posterior nerve-root ganglia of the spinal cord. These neurones subserve the transmission of afferent impulses from the lung. He states further that the ganglion nodosum contains multipolar cells giving origin to post-ganglionic fibres which are motor to the intrinsic bronchial musculature. The nature of the histological content of the ganglion nodosum gives weight to the experimental findings of Möllgaard. Work on the sympathetic supply to the lungs is somewhat uncertain; Möllgaard established the existence of efferent pathways from the spinal cord through the rami-communicantes albæ to the ganglion stellatum where there is a cell station; he also maintained that centripetal fibres pass to the second and third thoracic spinal ganglia and he deduced from this the possibility of the spinal cord mediating certain pulmonary reflexes.

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There is physiological evidence that afferent impulses play a part in the normal respiratory act. Adrian (1932), however, has shown that

the respiratory centre continues to discharge after all afferent impulses have been taken away by section of the vagi and curarization of the animal, by the observation of changes in electrical potential in the phrenic nerve in such a preparation. He points out that the respiratory rhythm obtained is not normal, and he has demonstrated by similar technique action currents in the peripheral end of the cut vagus corresponding to respiratory activity. This points to the stimulation of intrinsic pulmonary nerve-endings at each respiration.

The actual central connections of the vagus nerves and indeed the anatomy of the respiratory centre are far from clear. We know, from the work of Lumsden (1923) that there exist in the brain-stem structures to be correlated with certain components of the respiratory mechanism. By sectioning the brain-stem at various levels Lumsden argued the existence of an "apneustic" or gasping centre situated just cephalic to the striæ acusticæ and a "pneumo-taxic" or "apneustic inhibitory" centre at a higher level. Samson Wright (1934) in a recent review criticizes Lumsden's division of the respiratory centre and affirms that the centre exists as a co-ordinate whole. It is interesting to recall the words of Möllgaard in this connection: "Das Atmungszentrum stellt eine physiologische, nicht eine histologische Einheit dar. Darin haben die sensiblen Vaguskerne als Endpunkte der zentripetalen Lungen-nervern so wie die *Formatio reticularis* als Assoziationsgebiet eine besonders hervorragende Stellung."

PERSONAL RESEARCH.

The investigations undertaken were carried out on human lungs, but as it was impossible to apply *intravital* methylene-blue technique to the human subject, certain points were elucidated by the investigation of rabbit and rodent material. A variety of methods were employed. In the human material silver impregnation was used; the methods of Gross, Bielschowsky (for sections as described by Spielmeyer (1930)) and in addition Spielmeyer's (1930) method of staining medullated nerve in frozen sections of lung. Methylene-blue technique similar to that of Larsell was applied in the lungs of rabbits.

The nerves of the lung enter it at the hilum and are derived from the pulmonary plexuses. The components of the nervous supply are vagal and sympathetic, medullated and non-medullated. It is not possible to say with certainty on looking at a well-stained section of lung whether a particular nerve-fibre is of vagal or of sympathetic origin, but argument from general principle will often provide the answer.

The pulmonary nerves by the time they have reached the hilum of the lung have differentiated themselves into two distinct groups, those which are destined to supply the bronchial tree and those which subserve the innervation of the pulmonary vessels. Observation of these two systems has not revealed any interchange of fibres.

(1) *The bronchial plexus*.—The nature of this plexus is best demonstrated by thick sections in which a bronchus has been cut obliquely. There is a great wealth of nerve-fibres in the large and middle-sized bronchi, and a complicated interchange of fibres. The plexus exists far down the bronchial tree, at least to the terminal bronchioles. Further than this level I have not been able to demonstrate nerve-fibres. In the plexus are medullated and non-medullated nerve-fibres. The number of fibres demonstrable in a bronchus is proportional to the calibre of the plexus. One is so impressed with the ubiquity of this plexus in the middle-sized bronchus that it seems preferable to consider it as one plexus and not as divided into two, an intrachondrial and an extrachondrial. Apart from the general impression of a single plexus, closer study does not reveal any fundamental difference between that part which is internal to the cartilage plates and that which is external. There is a rich communication between the inner and outer nervous pathways. The general nature of the plexus is shown in figs. 1 and 2. The meshwork of the plexus is wider peripherally than centrally, and proximally than distally. Medullated fibres are much more frequent proximally and peripherally.

There are many nodes in the plexus which do not contain ganglion cells. Ganglia are, however, present at certain nodal points both in the outer and inner layers. The ganglion cells are multipolar and have long dendrites. With silver impregnation methods, as with methylene blue, I have not been able to demonstrate the pericellular basket work of the preganglionic fibres which Larsell (1921 and 1923) has shown in the rabbit. He found by methylene blue preganglionic pericellular baskets in the human lung but has not demonstrated them by Ranson's method. Further, the ganglion cells which he shows in the rabbit lung are spherical while those of the human are multipolar with long dendrites. The multipolar nature of these cells shows up particularly well in his Ranson specimen (Roger's modification). The last observation is amply confirmed in fig. 3. Ganglia exist on the course of the nerve-pathways apart from the existence of a node.

In the plexus there are both medullated and non-medullated nerves. At the nodal points there is great complexity of change and interchange

of fibres, making it impossible to trace a particular fibre for any distance. The medullated fibres frequently branch; this renders the picture confusing but may have physiological significance. The giving off of collaterals occurs at the nodes in the plexus. Further examination by means of medullated sheath staining shows that, whereas a number of fibres pass directly through a ganglion, others lose their medullated sheaths in it; the latter are apparently preganglionic to the cells of the ganglion in which they end. Sometimes, where a ganglion lies lateral to a trunk of the plexus, certain fibres pass by directly without any interruption in their medullated sheaths, while others lose their medullation. If all the medullated fibres in the section are well stained there is no reason to suppose that this appearance is an artefact, for it is unlikely that a single fibre should fail to stain merely in its course over a ganglion. It is a point of some importance that the medullated fibres which end in the ganglion enter it from opposed sides.

The following structures are innervated from this plexus; the epithelium, the bronchial musculature and the bronchial glands. I have been unable to demonstrate the ultimate innervation of the bronchial vessels, but judging from the richness of the capillary bed immediately below the basement membrane of the bronchial epithelium and the number of non-medullated fibres in it, I feel justified in concluding that this non-medullated network, which is a derivative of the plexus, has to do with the innervation of these vessels.

The epithelial innervation.—The bronchial epithelium is supplied by medullated fibres which lose their medullated sheath before passing through the basement membrane (fig. 4). Such a sensory fibre breaks up into a great number of small branches which have varicosities in their course (fig. 5). The nature of these varicosities is difficult to determine because their appearance varies with the degree of impregnation. In heavily impregnated specimens they appear much thicker than in those lightly stained and thicker as a rule in Ranson sections than in Bielschowsky preparations. This fact may be accounted for by a certain amount of general contraction of tissue due to imbedding in paraffin, since the Ranson sections were cut from paraffin blocks whereas the Bielschowsky specimens are frozen sections. I have frequently observed some fenestration of these varicosities as if they were actually reticula. The branching fibres of the endings ramify between the cells of the epithelium and end either freely or in small knobs. Here doubt may be expressed as to the actual nature of the knob-ending. The limitations of technique may mean failure to demonstrate a fibre beyond

the so-called knob. This doubt is expressed because, histologically, varicosities are very similar to "knob-endings." Considerable areas of epithelium are supplied by one nerve-ending, a point which is only realized in examination of sections tangential to the mucosa (fig. 5). It will be noticed in fig. 4 that certain of the basal fibres of the ending after coursing in the epithelium emerge and travel a short distance in the subepithelial fibrous tissue to re-enter the epithelium later.

Endings in plain muscle.—The derivatives of the bronchial plexus to the musculature of the bronchi are of two types, non-medullated fibres which are apparently motor and medullated fibres which are sensory. Larsell (1933) has shown, by means of methylene-blue technique, non-medullated fibres going to the plain muscle of the bronchi in the human lung, and a much more profuse non-medullated innervation of plain muscle in the rabbit lung (1921 and 1923). I have been able to confirm Larsell's observation in the rabbit, but have not been able to demonstrate by silver impregnation this nerve-supply in the human lung. The non-medullated nerve-supply to the muscle is shown to be derived from the parent plexus in fig. 6.

The main direction of these fibres is parallel to the long axis of the plain muscle cells. The individual fibres are finely varicose, and there is much free union between individual fibres. Some of the fibres end free without alteration in calibre. In the innervation of the plain muscle of vessels, Boeke (1933) has shown unassailably by Bielschowsky technique actual intracellular nervous processes which are derived from non-medullated fibres ramifying in the vessel wall. It is possible that, in the instance of bronchial musculature, the extracellular fibres have been stained alone and that their ultimate derivatives are not demonstrated by our methylene-blue technique.

The other nerve supply to the plain muscle of the bronchus is sensory. This has been discussed to some extent in dealing with the literature. In the present study I have observed the sensory innervation by means of the methods of Bielschowsky and Ranson. The specimen illustrated, fig. 7, was obtained by Bielschowsky impregnation, which defines more clearly than the Ranson method the morphology of the ending. The same disadvantages of paraffin imbedding apply here as in the case of the demonstration of intra-epithelial endings. In the Ranson method, although the reticula of the end nets are easily observed, there seems to be a heaping up of nervous substance, making the strands of the reticula appear much thicker than they appear in the Bielschowsky specimen. The ending is derived from a

medullated fibre of large calibre. Immediately after losing the medullated sheath the axis of the ending is guarded at its base by two nuclei, which may or may not be essential to this type of ending. The main stem gives off at right angles lateral branches; on these are networks, which show a main basket work with a secondary finer basket work in the main meshes. Close study of this ending reveals that these basket works are not inside the plain muscle cells and have no constant relation to their nuclei. A point which was not mentioned by Sunder-Plassmann is that the ending occurs at the branching of the plain muscle bands, and supplies the region of two or three of them. This ending is not confined to the region of plain muscle, for in the fibro-elastic tissue of the submucosa beyond the plain muscle there can be seen one or two end nets precisely similar to those seen in the region of the plain muscle. The significance of these findings will be discussed below. There can be no doubt that the ending is vagal in origin and that the impulses derived from its stimulation travel in the bronchial plexus and pass through the vagus.

Innervation of bronchial glands.—In this investigation it has not been possible to determine precisely the true nature of the innervation of the mucous gland. It is difficult, under any circumstances, to impregnate the nerves of a gland, but Larsell has, in his recent work, 1933, shown the innervation of the mucous glands to be non-medullated post-ganglionic fibres. I have some evidence of fine post-ganglionic fibres entering and ramifying in the fibrous septa of a glandular group, but I have never seen the actual endings inside the glandular cells, or on the cell membranes. It is therefore only conjecture to affirm, so far as this work is concerned, that the innervation of the bronchial glands is through the post-ganglionic fibres of the vagus.

The innervation of pulmonary vessels.—Here evidence is extremely scanty. In fig. 8 there is a fine medullated nerve-plexus running in the adventitia of the vessel—a branch of the pulmonary artery. There is no doubt that this is not the ultimate innervation of the particular vessel, but it represents something of the parent plexus. Its nature is similar to that described by Boeke.

In fig. 9 a sensory ending in the media of a pulmonary vein is illustrated. The method is that of Ranson, and it can be seen that the actual nerve substance is comparatively thick and grossly nodular. It is probable that sensory endings exist both in the pulmonary arteries and veins, since one can see occasional medullated fibres in their

adventitiæ, and for the additional reason that no ganglion cells are observed along the course of the vessels, a negative finding in which I find myself in accord with Larsell. Fig. 10 shows the presence of a single fine non-medullated fibre running in company with a capillary of the vasa vasorum of the pulmonary artery. There are a number of very fine reticula on the course of this nerve. The details are somewhat difficult to make out, but the assumption seems fair that this is the motor innervation to this particular capillary.

DISCUSSION.

Endings in plain muscle layer.—Emphasis was laid on the fact that the sensory ending, associated with the plain muscle of the bronchi occurred at the junction of the plain muscle bands. It is a well-known observation that the plain muscle of the bronchus is not a continuous sheet of muscle as the inner muscle of the intestinal wall. The bronchial musculature is arranged in bands in the form of an irregular net, so that, whereas a certain amount of the muscle runs transversely to the axis of the bronchus, there is a great part oblique to it, and muscle bands which are almost parallel to the long axis of the tube are frequently seen. The spaces between the muscle bands permit of the egress of the ducts of the mucous glands of the bronchi. The tendency during contraction of the bronchial musculature must be to cause shortening of the bronchial tree and possibly the invagination of the apex of a bifurcating bronchus inside the lumen of the parent stem. (See diagram 11.) In normal respiration, inspiration, with increase of chest capacity, distends the lungs, pulls out the bronchi and as a natural result tends to stretch the bands of bronchial muscle, thus widening the meshes of the plain muscle network. In so doing the maximal stimulation of the sensory ending will occur at the height of inspiration.

Although the foregoing is conjecture, it seems that we have in the bronchial tree a nerve-ending admirably adapted to receive the stimuli of stretch. The work of Sunder-Plassmann, although he did not recognize the relationship between the branching muscle bands, points in the same direction; Larsell, who has called these sensory endings "plain muscle spindles," appears to be in agreement with my observation. Morphologically the same type of ending has been demonstrated in the carotid sinus by Sunder-Plassmann and it is natural to conclude that, granted specificity of function for similar histological structures, these endings can only transmit stimuli arising from tension which is the only conceivable stimulus common to the carotid sinus and the

bronchial tree. Another point in favour of tension being the stimulating agency is that these endings are situated in the bronchial musculature at the point of division of a bronchus, where the amount of movement is presumably greatest.

Returning now to the thesis that the maximal stimulation of this particular ending is at the height of inspiration we are justified in assuming that the physiological significance of stimulating this ending is to cause inhibition of the inspiratory phase and the consequent initiation of expiration—the Hering-Breuer reflex—by the passage of afferent stimuli through the vagus to the respiratory centre. There is,

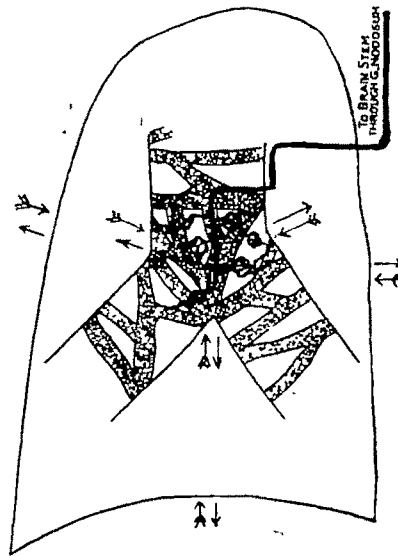


FIG. 11.—Diagrammatic representation of the significance of the sensory innervation to the plain muscle layer. The untailed arrows represent the direction of application of force in inspiration, the tailed arrows show the influence of expiration.

Note that contraction of the plain muscle acts in a direction similar to the forces of expiration. Narrowing of the bronchial lumina by spasm necessitates a much greater inspiratory pull before the sensory ending can be stimulated.

of course, according to Larsell, another ending which might be the source of the Hering-Breuer reflex, the alveolar ending. This ending I have not been able to demonstrate, but from a consideration of the morphological uniqueness of the endings in the plain muscle layer and from the nature of the endings which Larsell illustrates as occurring in the alveolar walls, it seems that the former are more likely to be the afferent end of the Hering-Breuer arc. Sunder-Plassmann, in discussing the significance of this ending suggests that stimulation of

it in bronchial spasm is responsible for many of the symptoms of bronchial asthma. It seems to me, however, more logical to assume that stimulation of these endings does not occur in such a condition as bronchial asthma, as the contraction of the bronchial musculature prevents stretching of the bronchi during inspiration (fig. 11); a much deeper inspiration is required before the bronchial spasm can be overcome. The suggestion is therefore made that, in addition to the mechanical difficulty of expiration in bronchial spasm, there is a nervous upset. Bronchial spasm causes a decrease in the bronchial lumen which is probably more marked at the points of division of the bronchi. In inspiration the increase in capacity of the chest acts in a direction contrary to that of the contracted plain muscle, and hence the comparative freedom of inspiration in the asthmatic. In expiration, diminution in chest capacity along with the constricting force of the musculature in spasm effectively diminishes the bronchial calibre, and in this manner causes the mechanical difficulty of the expiratory phase. It is almost a platitude to say that asthmatics find the whole course of expiration difficult, not merely the mechanical expulsion of air from the lungs but the very initiation of the movement. This difficulty in the initiation of expiration can be most easily explained by the assumption of a disorder of nervous function. Before stimulation of the endings in the smooth muscle bands can occur a deep inspiration has to take place; this is the explanation of the fact that the asthmatic must inflate his chest to an extreme degree before expiration will occur automatically; in fact, expiration may become a voluntary act in the absence of afferent impulses from the plain muscle of the bronchial wall.

The epithelial endings.—These endings are, as has been described, actually in the epithelium and must therefore receive impressions from the epithelium. It is impossible to say definitely in what function these impressions are concerned. It is known that stimulation of the bronchial epithelium will cause coughing, and it seems natural to conclude that the afferent pathway for this reflex arises in these intra-epithelial endings and passes through the sensory medullated pathways of the vagus, by way of the ganglion nodosum to the brain-stem. These endings cross and recross the basement membrane and branches are often formed immediately after the axis cylinder loses its medullated sheath. The conclusion may be drawn that, in a pathological process which causes the shedding of bronchial epithelium, a large number of bare axis cylinders of sensory nerves will be exposed. Hence follows the tendency to

coughing and the causation of other effects which will be discussed below.

The bronchial plexus.—In the bronchial plexus there are large numbers of medullated nerve-fibres. These may be : (1) Pre-ganglionic fibres of the vagus ; (2) sensory fibres of the vagus ; (3) pre-ganglionic fibres of the sympathetic ; or (4) the collaterals of the pre-ganglionic or sensory fibres of the vagus. If the third possibility exists at all it must be very rare. As the motor and secretory functions of the vagus are mediated through bronchial ganglia, preganglionic fibres of this nerve must constitute a part of them. The number of sensory fibres of the vagus must be considerable and can be assessed with some degree of accuracy owing to the observation of medullated fibres giving rise to sensory endings in the bronchial epithelium and musculature. It is doubtful if many of these fibres are collaterals of the preganglionic and sensory fibres of the vagus, but direct observation shows a very great deal of branching of medullated fibres.

It is impossible to determine the true state of affairs, but, as the frequency of branching of medullated nerves in the internal part of the plexus is apparently as great as that which occurs peripherally in respect of a bronchus, and since ganglia are more numerous peripherally, the peripheral branching may be an expression of the division of pre-ganglionic fibres, while the branching occurring underneath the epithelium is much more likely to be accounted for by the branching of sensory fibres. In point of fact the actual collateral branchings of medullated nerves which are undoubtedly sensory can be made out very frequently. It may therefore be concluded that some part is played by collateral branches of the sensory nerves to the epithelium and musculature in making up the complex picture of a skein of medullated fibres in the bronchial wall. The significance of these collateral branches has yet to be determined. It is unlikely that a single fibre gives rise to several sensory endings. If such were the case, then the medullated collateral of a sensory fibre takes a curious course to reach its ending. It is more probable that these medullated collaterals of sensory fibres are "intrinsic pre-ganglionic fibres." The whole scheme of the intrinsic innervation of the lung seems to point to a wealth of axonic reflexes, particularly from the epithelium. Diagram 12 shows a sensory fibre with three collaterals ending in the epithelium. The drawing has been made from an actual specimen, and the continuity of the collateral fibres was definitely established. The most peripheral collateral is non-medullated and travels directly to terminate in the subepithelial capillary network,

the other two travel to the bronchial plexus. The natural conclusion is that the stimulation of a sensory ending, as shown in this diagram, will, by means of a direct axon reflex, cause a capillary response at the actual level of stimulation, and that collateral fibres travelling through the plexiform network will so act on the nodal ganglia as to cause a much more extensive intrinsic response. Since the bronchial ganglia are responsible for the innervation of the bronchial musculature and of the mucous glands, collateral fibres of sensory nerves ending in the ganglia should produce ultimate effects on the structures innervated by the

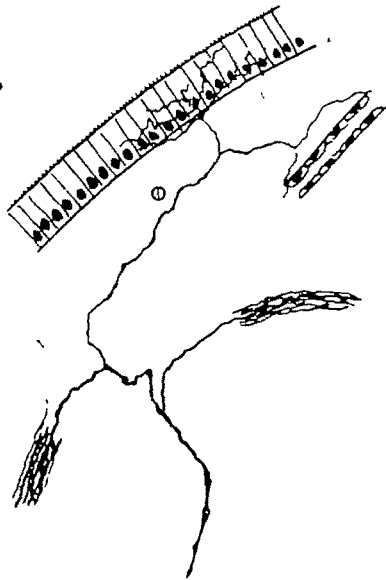


FIG. 12.—Collaterals of a sensory fibre going to the epithelium. The most peripheral fibre goes directly to the sub-epithelial capillaries. The other collaterals go to the bronchial plexus and hence have the possibility of acting as "intrinsic preganglionic fibres" to influence ultimately the bronchial musculature and mucous glands.

ganglia. Morphologically it is possible for axon reflexes arising in the sensory fibres to the bronchial epithelium to have far-reaching responses. Thus a noxious stimulus applied to the bronchial epithelium will cause not only the centrally produced effect of coughing, but also extensive intrinsic reactions, such as a widespread secretion of mucus, and possibly something of a peristaltic action on the part of the bronchial musculature. These extensive intrinsic effects I believe to be of the nature of axonic reflexes from the sensory endings of the vagus mediated through medullated collaterals which go to the ganglia of the bronchi and thus make possible co-ordinate and extended responses.

SUMMARY.

I. An investigation was undertaken to demonstrate the intrinsic nervous mechanism of the lungs, the subject being approached from the point of view of histology.

II. The bronchial plexus is described as being essentially a single plexus, ganglionated at certain of its nodes.

III. Sensory endings are described in the epithelium of the bronchus, in the plain muscle layer and in the pulmonary vessels.

IV. The motor innervation of the bronchial musculature as described by Larsell has been confirmed.

V. The parent plexus of the vascular innervation of the pulmonary vessels has been demonstrated and described.

VI. Certain conjectures are made with regard to the physiological significance of: (a) Endings in the plain muscle layer; the Hering-Breuer reflex; a contribution is made to the explanation of the symptomatology of asthma. (b) The significance of the epithelial endings is discussed, and the effects of stripping of the epithelium are mentioned. (c) The possibility of axon reflexes is discussed.

This work was undertaken firstly as Carnegie research scholar in the University of Glasgow, and secondly as Faulds Fellow in Medicine. My thanks are due to the administrators of these Scholarships. I have to express my great indebtedness to Professor E. P. Cathcart, for his constant interest in this research and for the benefit of much good advice during the investigations.

I wish to thank Dr. J. W. S. Blacklock of the Pathology Department of the Royal Hospital for Sick Children of Glasgow, for the provision of human material, and also to thank Dr. J. G. Greenfield, of the National Hospital, Queen Square, London, for photographing my preparations.

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DESCRIPTION OF PLATES VII AND VIII.

FIG. 1.—Bielschowsky method. (Human.) Non-ganglionated nodes of the bronchial plexus.

FIG. 2.—Spielmeyer's method for medullated nerve. (Human.) Extrachondrial region. Thick bundles of medullated nerve, part of the bronchial plexus, demonstrate the wealth of medullated nerve in the bronchi.

FIG. 3.—Bielschowsky method. (Human.) Ganglion from extrachondrial region, showing multipolar ganglion cells with long dendrites.

FIG. 4.—Bielschowsky method. (Human.) Bronchial epithelium, sensory ending; note the curious course of the fibres about the basement membrane.

FIG. 5.—Bielschowsky method. (Human.) Tangential section of the bronchial epithelium. The extent of epithelium innervated by a single ending is demonstrated here. Note the varicosities on the branching fibres and their undoubted intra-epithelial ramifications.

FIG. 6.—Methylene blue. (Rabbit.) The fine varicose fibres forming a plexus round the plain muscle bands represent the motor innervation of the bronchial musculature. Note the continuity between this plexus in the plain muscle and the parent plexus, part of which is seen at the bottom of the picture.

FIG. 7.—Bielschowsky method. (Human.) Sensory ending in plain muscle layer. Note the disposition of the plain muscle bands relative to the ending. Only one of the basket-work expansions of the ending is in focus.

FIG. 8.—Methylene blue. (Rabbit.) Pulmonary artery, fine varicose fibres in the adventitia of a vessel.

FIG. 9.—Ranson method. (Human.) Pulmonary vein. Parts of a sensory ending are seen in the media of the vessel. The section is from a paraffin block and therefore no great extent of the ending is seen.

FIG. 10.—Gross method. (Human.) Fine non-medullated nerve in a capillary wall.

PLATE VII.



FIG. 1.



FIG. 2.



FIG. 3.

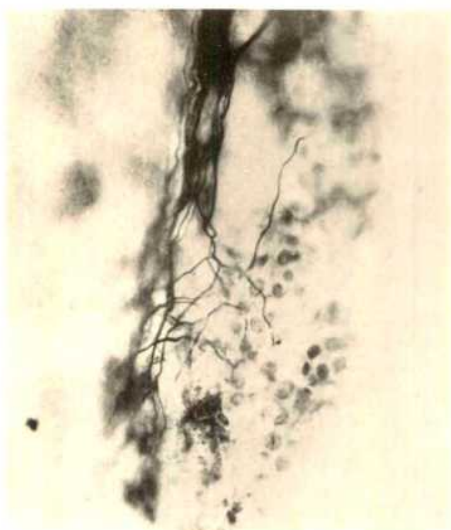


FIG. 4.

To illustrate paper by John B. Gaylor.



FIG. 5.



FIG. 6.

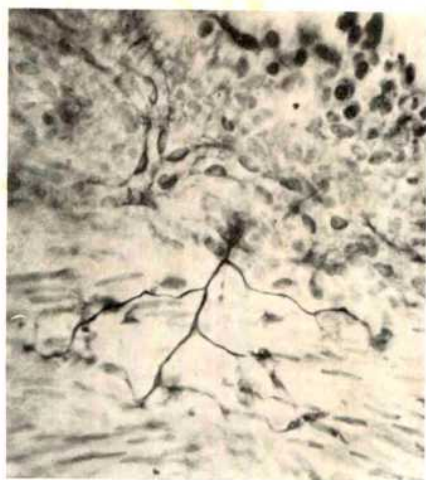


FIG. 7.



FIG. 8.

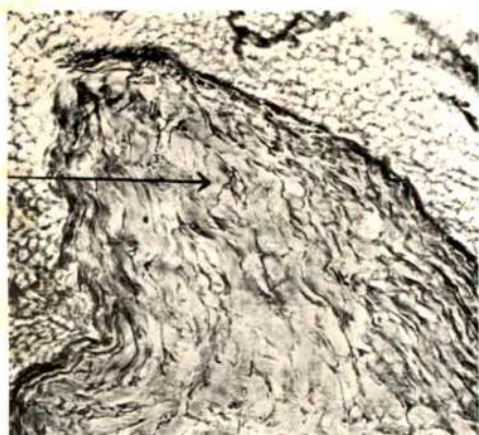


FIG. 9.



FIG. 10.

To illustrate paper by John B. Gaylor.

SUBACUTE SPINO-CEREBELLAR DEGENERATION OCCURRING IN ELDERLY PATIENTS.

BY J. G. GREENFIELD.

(From the National Hospital, Queen Square, London.)

WHILE no type of nervous disease presents itself constantly in a stereotyped form, some have a special tendency to vary from their main type. Among the latter the spino-cerebellar ataxias are conspicuous. Even Friedreich's ataxia, which might be considered as the prototype of this class, varies greatly both in its clinical course and in its incidence on the spinal tracts and the cerebellar connections. In fact, each affected family seems to present its own variant of the disease. This tendency is even more marked in the rarer cases of cerebellar ataxia which come on in the middle or later years of life. Of these the best-established forms are olivo-ponto-cerebellar atrophy and parenchymatous cortical cerebellar atrophy. Occasional variants of these have been described. For example, the red nuclei with or without the dentate nuclei may be affected and the pontine nuclei spared, and minor degrees of degeneration may be found in the spinal cord. Further, the cerebral cortex may be involved in the degeneration.

The reason for describing the following cases is to indicate a further variant, which differs in many respects from the types that have previously been recorded, but is closely allied to them in others. The cases are of interest also in their close resemblance to one another both in their clinical and their histological features. While it seems unlikely that so unusual a pathological picture could have been missed in the past, the occurrence of these two cases in one hospital within two years of one another makes it likely that this variant of spino-cerebellar degeneration is not a mere sport, and that other cases of this type will crop up from time to time.

I owe the pathological material in the first case to Dr. Symonds' interest and enterprise, and I should like to take this opportunity of thanking him and Dr. Adie for their permission to use the clinical records.

Case 1.—E. H., aged 66, an unmarried woman, was admitted to the National Hospital under Dr. C. P. Symonds, on June 8, 1931. Apart from a

small tumour in the left breast which had been removed in July, 1930, she had always been in good health. Towards the end of April, 1931, she noticed occasional numbness in the left thumb and a few days after this she felt weak and had difficulty in walking. On May 9 she went to bed, and after staying there for a week she had difficulty in getting out of bed. During this time numbness of the thumb still bothered her. About May 20 she felt very weak in both legs, especially the left, and her left arm was also weak. At the end of May her speech became affected in that words were uttered one at a time. About the same time she experienced sensations of dizziness and swimminess. Since then she had become weaker and drowsy and had occasional difficulty in breathing. When seen in hospital she was a thin emaciated woman with a rhythmical tremor of the head. She spoke in a sing-song scanning manner; her voice soon tired and fell to a whisper. There was some drooping of the eyelids. On full lateral deviation of the eyes to either side a few nystagmoid jerks were seen and if an attempt were made to hold the eyes in this position for a few seconds, they moved slowly upwards and to the left, returning to their previous position with a quick jerk. These oblique upward movements were more pronounced on looking to the extreme left. The tongue was protruded slightly to the right and was coarsely tremulous. The left arm was weaker and clumsier in its movements than the right; it was hypotonic and very ataxic. A less degree of ataxia was found in the right arm. The left leg also was relatively weak and was slightly ataxic in heel-to-knee tests. There was a remarkable asymmetry of the deep reflexes. The triceps jerk was faintly present on the right and absent on the left; the biceps jerk present on both sides and the supinator jerk absent on the right and present on the left side; the knee-jerk was present on the right and exaggerated on the left and the ankle-jerk present on the right and absent on the left. The upper abdominal reflexes were present, but the lower absent; extensor responses were obtained from the soles of both feet. Superficial sensation was normal. There was some loss of sense of position of the legs on movement at the larger joints, although movements of the fingers and toes were normally appreciated.

Dr. Symonds has kindly sent me the following note on her mental state:—

"My note on this patient when I first saw her includes the observation that she was facile and emotional. Her speech was scanning and slow but there was no aphasia. After she was admitted to hospital she became drowsy, but could be roused to answer questions. She proved then to be disoriented and confused. At times she was relatively lucid but always showed gross defect of memory and imperfect attention together with a somewhat childish euphoria."

A lumbar puncture was performed on June 9. The cerebrospinal fluid was clear and colourless. It contained 30 lymphocytes per c.mm., and 0.1 per cent. of protein and gave positive Nonne-Apelt and Pandy reactions. The Lange reaction gave a strong curve of the paretic type 5.5.5.5.5.5.4.4.3; this was confirmed by De Thurzo's bicoloured guaiac test which gave a result of 0349442100, an unusually strong reaction for a non-syphilitic fluid. The Wassermann reactions of blood and cerebrospinal fluid were negative. This

result appeared to make the diagnosis of disseminated sclerosis the most probable, although the patient's age was against this diagnosis.

While in hospital she became steadily worse. The tremor of the head and the ataxia of the arms became more severe, and the speech more affected, the nystagmus remaining as before. She left hospital on July 16 for her home, where she died on August 4, having been ill altogether for just over three months.

The brain and spinal cord were removed for examination about twenty-four hours after death. They presented no abnormality to the naked eye. Pieces from each spinal segment, from various levels of the brain-stem, and from the basal ganglia and various parts of the cortex were examined by a variety of histological methods. The Busch modification of Marchi's method was successfully applied to the cord and brain-stem, and revealed a widespread tract degeneration in the spinal cord, affecting all the long tracts in varying degree. In the brain-stem the only degeneration found was in Gower's tract, of which all the systems, spino-cerebellar, spino-tectal and spino-thalamic, presented some degree of degeneration. In the uppermost segments of the midbrain the strio-Luysian fibres as they crossed the outer third of the crus were degenerated, but neither here nor in the pons was there any sign of degeneration of the pyramidal fibres. The highest level at which we found definite evidence of degeneration of this system was at its decussation at the lower end of the medulla oblongata. Where posterior roots were included in the sections of the cord, evidence of myelin degeneration was found in them. This was greatest at the level of the cervical enlargement, and was least in the thoracic segments of the cord. Similarly, the degeneration in the columns of Burdach was more severe than in the columns of Goll. The degeneration in the posterior columns was more extensive in the lumbar segments than at the mid-thoracic level and was most advanced in the middle root zone. The ventral pyramidal tract was also degenerated in sections at the cervical and mid-thoracic levels.

In sections stained by Herxheimer's scharlach R and hæmatoxylin it was possible to form an estimate of the relative duration of the degeneration in the various tracts of the cord. In the anterolateral columns at all levels the degeneration was recent, appearing only as patchy swelling of some of the myelin sheaths, without any fat granule cells or droplets of brightly staining fat. In the posterior columns the columns of Burdach in the cervical region contained many fully developed fat granule cells filled with red staining lipid, but very few of these had reached the perivascular spaces. A smaller number of such cells was seen in the dorsal columns of the lumbar enlargement. Elsewhere in the dorsal columns the degeneration was rather slighter and earlier than in the pyramidal and cerebellar tracts.

When the cerebellum was examined by this method, numerous fine fatty droplets were seen in the innermost zone of the molecular layer and scattered among the granule cells. Similar lipid granules were seen round many of the vessels in the white matter, and a few also lay among the myelinated fibres in

this situation, increasing in number as one approached the dentate nucleus. The most striking alterations in the cerebellum were, however, demonstrated by hæmatoxylin and by Nissl's method. By these it was seen that the Purkinje cells had completely disappeared from most of the cerebellar folia, so that only here and there could an isolated and severely degenerated cell be found.

There was probably also some loss of granule cells, as they were less compactly arranged than normally. There was no shrinkage of the molecular layer and no loss of basket fibres could be made out in sections stained by Bielschowsky's method. The dentate nuclei were normal, as were all the nuclear centres in the brain-stem, with the exception of the nucleus of Luys, in which there was a considerable loss of cells (fig. 5) in the dorsolateral half. Many of the remaining cells, especially in this part of the nucleus, were degenerated, their nucleus being subcapsular and their cell body shrunken away from its bed and devoid of Nissl granules.

Throughout the cerebellum there was considerable, diffuse lymphocytic infiltration of the meninges and an infiltration with similar cells was seen round many of the vessels of the white matter both near the cortex and more deeply. Among these lymphocytes were a few cells which contained fatty granules, but the great majority were free from such inclusions. A few plasma cells could be identified among the lymphocytes.

A similar infiltration was seen round a few vessels in the brain-stem in certain situations. Thus several vessels in the outer third of the pons at the uppermost levels of the mid-brain were infiltrated, but no infiltration of the more dorsally placed vessels was found. In the pons there was slight cuffing of some small vessels lying among the pyramidal fibres and among the fibres of the fillet. In the medulla cuffing of the vessels in the pyramids increased on passing downwards. There was also slight infiltration in the neighbourhood of Gower's tract and in the nuclei of the dorsal columns. None was found at this level in the fillet or the olivary nuclei.

In the spinal cord the infiltrations were both more intense and more extensive. Many vessels at all levels were surrounded by several layers of cells, most of which were lymphocytes with an occasional plasma cell and a few small cells containing fatty granules. In addition, there were numerous "inflammatory nodules" both in the white and grey matter, most of which seemed to bear no relation to any vessel, although some lay near to a perivascular infiltration. These were composed chiefly of microglial cells, many of which were undergoing karyorrhexis with, in addition, some larger reniform nuclei resembling those of endothelial cells. An occasional plasma cell could also be identified in relation to these nodules.

The meninges were diffusely infiltrated at all levels, but most severely around the cervical enlargement. This meningeal exudate was, however, slight by comparison with the degree of perivascular cuffing, and in many of the thoracic segments was hardly noticable. Infiltration of the dorsal roots was rather more severe, and took the form both of a diffuse cellular increase along

the line of the fibres and of focal collections of cells in the neighbourhood of the vessels. This also was greatest in the cervical segments and least at the thoracic level.

Neuroglial overgrowth was nowhere severe. There was some thickening of the neuroglial network on the lateral surface of the cord in the region of the spino-cerebellar tracts and in the dorsal columns in the areas of greatest degeneration. The radially disposed fibres in the molecular layer of the cerebellar cortex were also thicker and more apparent than normal, but there was no increase in their number, and no definite neuroglial overgrowth could be made out in other parts of the cerebellum.

SUMMARY OF CASE 1.

A woman, aged 66, began to suffer, three months before death, from numbness in the left thumb and weakness of the legs. The legs and the left arm became rapidly weaker and the speech became scanning in type. At the same time she had sensations of dizziness and became mentally somewhat childish. When examined a month before her death there was a rhythmical tremor of the head, a sing-song, scanning speech which tired quickly, coarse tremor of the tongue and slight indefinite nystagmus on lateral deviation of the eyes. The arms and legs were hypotonic and ataxic with asymmetry of the deep reflexes, and plantar responses of extensor type. Apart from some loss of the sense of position her sensory system was intact. The cerebrospinal fluid contained a considerable excess of cells and protein and gave a "paretic" type of colloidal gold curve. Post-mortem examination revealed early degeneration of the dorsal roots, the dorsal columns of the cord, especially the middle root zone, the spino-cerebellar tracts, and the pyramidal tracts from the medulla downwards. In the cerebellum there was almost complete loss of Purkinje cells with no loss of granule cells or of cortical nerve-fibres. There was also degeneration of the nucleus of Luys and of strio-Luysian fibres passing across the outer third of the crus. Intense perivascular infiltration was found in all areas where tract degeneration was in progress.

Case 2.—F. L., aged 57, was admitted to the National Hospital, Queen Square, on December 14, 1932, under Dr. Adie.

Except for an attack of gout at the age of 50, he had enjoyed good health until two months before admission when he began to have shooting pains in his right calf. These were severe and were associated with much sweating. Two or three days later a similar pain began to be felt in the left leg. A month later the right leg, in which the pains had all along been worse, began to feel weak and this was followed in a few days by similar weakness of the

left leg, so that by November 25 he had to take to bed where he had since remained. The pains had become progressively worse, and his legs were so weak that he could only walk a few steps. On the day before admission the soles of his feet tingled when he stood on them. He had been losing weight and was rather short of breath on exertion for the last few months before admission to hospital.

On examination he was found to be alert, attentive and co-operative and his memory was unimpaired. Apart from some myopia his special senses were intact and the functions of the cranial nerves were unimpaired. His arms were thin, the small muscles of the hands appearing specially wasted and weak. There was no alteration of tone or of motor power in them and the finger-to-nose tests were well carried out. The muscles of the legs appeared very flabby and somewhat wasted, especially the quadriceps group of the right thigh in which some coarse fascicular tremor was noticed. The deep reflexes of the upper limbs were very brisk; the right knee-jerk was absent and the left very feeble, and both ankle-jerks were absent. The abdominal reflexes were somewhat reduced on the right side and both plantar reflexes were flexor in type. His gait was very ataxic. The feet were sometimes lifted high and sometimes dragged along the floor, and he swayed grossly unless supported even with his feet well apart. Closure of the eyes greatly increased his unsteadiness. There appeared to be some analgesia and loss of thermal sensibility over the outer side of the lower half of the right leg. His chest was rather dull on percussion all over and the breath sounds were bronchial in type at the apices, but without adventitious sounds.

A lumbar puncture performed on December 15 gave a yellowish fluid at an initial pressure of 120 mm. On standing it formed a cobweb coagulum. It contained 120 cells per c.mm., of which 7 per cent. were large mononuclears and the rest lymphocytes, and 0.45 per cent. of protein with strongly positive globulin reactions. Lange's gold sol test gave a reaction in the higher dilutions only, 0000112122. The Wassermann reaction was negative in both cerebrospinal fluid and blood.

Examination on February 13, 1933, showed considerable increase in his symptoms. He had no energy and seemed unable to help himself in any way. His arms were thinner and much weaker, but no fibrillation could be seen in them. He could not assume or retain a sitting posture. The legs were more wasted and there was bilateral drop-foot, and great general weakness of all the leg muscles. Fibrillation was present in all the leg muscles. The deep reflexes were brisker in the left arm than in the right; the left knee-jerk was present but the right knee-jerk and both ankle-jerks absent. The abdominal reflexes were now absent on the left side and the left plantar was of Babinski type. No definite defect of sensibility could be made out.

Examination of the cerebrospinal fluid at this date showed it to be colourless, but forming a heavy flocculent coagulum on standing. It contained 18 lymphocytes per c.mm. and 0.12 per cent. protein with positive globulin reaction. The Lange and Wassermann reactions were similar to those found previously.

A month later, on March 16, he was noted to be generally worse, unable to do anything for himself and incontinent of urine and faeces; but this appeared to be due rather to mental than to physical deterioration. His voice was soft, slurred, mumbled and almost inaudible, and it was impossible to get him to make any definite statement as to how he felt. Examination at this date showed the cranial nerves to be normal as before. *No nystagmus* was present. There was some fibrillation and increase of tone in the arms, with great weakness. The muscles of his flanks bulged when he coughed. The legs were rather more wasted and weaker, and some fibrillation was noted in the quadriceps and calf muscles. The plantar reflexes were now both extensor.

From this time until his death he went rapidly downhill. He made no attempt to speak, but merely grunted and groaned. He had to be fed and was incontinent of urine and faeces. That there was some power of movement of all the limbs was evident when he was disturbed, but he made no spontaneous attempts to use them. His face was quite expressionless, with the mouth wide open, but he grimaced when subjected to any unpleasant disturbance. The legs were kept flexed at the knees and rotated outwards at the hips, and any attempt to straighten them met with opposition. On May 4 the deep reflexes were active in the arms, especially on the left side, but absent in the legs. He reacted to pinprick to all skin areas. The percussion note over the right base was now dull with diminution of breath sounds and a few scattered rhonchi. He died on May 9, 1933, having been ill for about seven months.

A post-mortem examination was performed within twenty-four hours of death. A small gland could be felt in the left axilla and a mass of glands low in the neck to the right of the trachea. Examination of the chest showed a large mass of glands lying in front of and behind the trachea at its bifurcation and extending upwards to the root of the neck. A small flat nodule of cancer about 1.5 cm. in diameter lay on the front of the thymus where it covered the pericardium. The root of the left lung was extensively invaded by white cancerous growth, a small nodule of which projected through the mucosa of the main bronchus. Retention of purulent fluid in the bronchi beyond this had led to early bronchopneumonic changes. The right lung was unaffected. Apart from some calcified mesenteric glands and a considerable degree of perisplenitis, the other organs were healthy.

The tumour at the base of the left lung proved histologically to be a bronchial carcinoma composed of masses of elongated darkly staining cells. Although in most parts of the growth these cells had no definite arrangement, they had a tendency, where they lay near the bronchial wall, to be disposed radially to the surrounding connective tissue. Numerous mitoses gave evidence of rapid growth.

Examination of the nervous system by the same methods as those used in Case 1 showed lesions which, although differing in certain particulars, had a remarkable similarity to those already described. Busch's method showed degeneration in all the long tracts of the cord, most intense in the direct spino-cerebellar tracts and also affecting the ventral spino-cerebellar tracts, the

pyramidal tracts and the middle root zone of the dorsal columns fairly severely. Elsewhere it was slight and early. In the medulla, in addition to these tracts, the internal arcuate fibres with the fillet, and the fibres passing inwards from the vestibular nuclei to form the posterior longitudinal bundle, were the seat of early degeneration. The pyramidal fibres became more affected as one passed down the length of the medulla, but were less intensely degenerated than in the cord. An isolated degenerated fibre passed into the hilum of the olive, but this system was remarkably free from degeneration.

In the pons, early degeneration was found in the fillet, the posterior longitudinal bundles and the pyramidal bundles. In the latter it was quite slight, affecting only a small proportion of the fibres. The transverse fibres of the pons were quite free from degeneration, but there was some rather diffuse early degeneration of individual fine fibres in the tegmental area. Both superior cerebellar peduncles were here degenerated. On the left side the degeneration was very severe and evidently of some standing, whereas on the right it was only a degree more intense than in the fillet and posterior longitudinal bundles. These degenerations could be traced into the mid-brain where the stratum profundum outlining the grey matter round the iter showed definite degeneration. There was also at this level a collection of degenerated fibres in the outer part of the stratum intermedium probably representing efferent fibres from this part of the corpus Luysii. The latter nucleus stained intensely black in its outer two-thirds and dense bands of fibres could be seen passing into it, most of them crossing the internal capsule at the junction of its middle and outer thirds. A smaller number were seen curving round the outer border of the crus to join the capsule of the corpus Luysii. Early degeneration was also seen at this level in the fasciculus thalamicus (fig. 6). Only a few darkly staining fibres could be seen in the substantia nigra. The pyramidal fibres at this level were even less affected than in the pons.

In the basal ganglia the only evident degeneration was in an area in the middle of the outer zone of the globus pallidus. Isolated black fibres were also seen in the white matter underlying the precentral gyrus.

With Scharlach R and hæmatoxylin it was very difficult to see any evidence of degeneration in the majority of the less affected tracts, although examination with crossed Nicol prisms showed bright crystals and granules in all the areas where Marchi degeneration was seen. The outer part of the nucleus of Luys however contained, in addition, definite fat-granule cells, and isolated fatty cells could be seen in the strio-Luysian fibres passing across the crus. In the mid-brain the superior peduncle on the left side was a mass of tightly packed fat-granule cells, and these could be traced into the hilum of the left dentate nucleus. The pyramidal fibres began to show definite alterations to Scharlach staining in the lower half of the medulla where some of the fibres were swollen and stained rather more brightly than normal. In the cord they became progressively more degenerated, but no definite fat-granule cells could be found in them at any level.

The dorsal spino-cerebellar tracts, by contrast, were almost completely

degenerated, the myelin from their fibres having been absorbed in fat-granule cells which were already being collected in perivascular spaces. In the dorsal columns there was a general sparsity of fibres, especially in the columns of Goll, and fairly numerous fat-granule cells were found in the middle root zone throughout the cervical and upper thoracic segments. In the lower thoracic and lumbar cord, although early degeneration was evident and was greatest in the middle root zone, no fat-granule cells were seen.

In the cerebellum scattered fatty granules could be seen at the junction of the molecular and granular layers. These were rather more definite in the vermis than in the lateral lobes, but were nowhere so abundant as in Case 1.

The changes in the nerve-cells were studied in sections stained with toluidin blue and by Bielschowsky's silver method. In the cerebellar cortex the loss of Purkinje cells was considerable, but was not nearly so complete as in Case 1. While many foliæ devoid of Purkinje's cells were seen in every section examined, there were also areas in which the number of these cells approximated to the normal. As far as could be made out there was no special incidence of this degeneration on any portion of the cerebellar cortex; the vermis was possibly rather more affected than the lateral lobes, but numerous Purkinje cells were seen in it also. Many degenerated Purkinje cells were also seen, but the majority of those which remained appeared fairly healthy. No lipid was present in any of these cells. There was a relative preservation of basket fibres, as empty baskets could be seen in many places, but the poverty of these structures in the most affected foliæ suggested that they had eventually degenerated. The tangential fibres of the molecular layer were well preserved, and there was no apparent loss of granule cells or of mossy or climbing fibres; nor were any axonal swellings found in the layer of granules. The dentate nuclei were degenerated, especially on the left side where the majority of the cells had disappeared. There was here a great excess of microglial nuclei, which appeared to be due to degeneration of the fibres of the superior peduncle. Neuroglial overgrowth in the cerebellum was limited to a thickening of the radial fibres in the molecular layer and a slight excess of fibres in the white matter, especially round the vessels. A denser gliosis was seen round the left dentate nucleus. The nerve-cells of the nuclei pontis, the red nucleus and the substantia nigra appeared to be unaffected, although they contained a slight excess of lipid. The nucleus of Luys, on the other hand, contained no nerve cells in its dorsolateral part, and considerably less than normal in its ventro-internal part, many of the remaining nerve cells being degenerated. In sections stained by Bielschowsky's technique the outlines of the nucleus could be easily made out from its rich network of capillaries, and the loss of nerve cells was very evident (fig. 4). In sections stained by Nissl's method a great excess of small nuclei was seen in this part of the nucleus. These were chiefly of microglial origin and represented the early stages in the formation of fat-granule cells. An overgrowth of neuroglial fibres was also found in this area.

No definite abnormality could be made out in the cells of the basal ganglia, although here also some excess of lipid was present. The frontal, Rolandic,

parietal and hippocampal regions of the cerebral cortex were examined, but no abnormality in the appearance or the arrangement of nerve-cells could be seen.

In the medulla, no loss of nerve-cells could be made out. Both the olives and the arcuate nuclei appeared healthy.

In the spinal cord a very definite loss of cells was seen in Clarke's column. In each of the thoracic segments it was reduced to one, or at most two, cells on either side, and in many sections these were shrunk and full of lipid. But in no section examined was there complete absence of these cells on both sides. The anterior horn cells were normal in number and size, but many of them also contained an excess of lipid. No definite abnormality was found in the cells of the dorsal root ganglia.

Perivascular infiltration was as intense in this case as in Case 1, and was rather more extensive. It was found at all levels of the spinal cord, especially in the grey commissure and in the dorsolateral tract of the cord. It was perhaps most evident in the region of the dorsal spino-cerebellar tracts, but was by no means confined to this area. Meningeal infiltration was much slighter, and appeared to be secondary to the affection of the intramedullary vessels. Infiltration of the dorsal roots was not conspicuous. In the medulla some vessels near the floor of the fourth ventricle were affected. In the pons the most evident infiltration was in the tegmentum, especially in relation to the left cerebellar peduncle. But both here and in the midbrain many vessels in all areas were surrounded by a cuff of cells. Very little infiltration was found in the white matter of the cerebellum, but several vessels in the neighbourhood of the dentate nuclei were affected. There was fairly heavy infiltration of several vessels in the globus pallidus, and a few in the putamen and the lateral nucleus of the thalamus were surrounded by a single ring of cells. No infiltration was found in most regions of the cortex, but one vessel in the cornu ammonis and one under the Rolandic cortex were affected. As in Case 1, the infiltration consisted chiefly of lymphocytes. Plasma cells were scanty, and very few fat-containing cells were seen.

SUMMARY OF CASE 2.

A man, aged 57, who suffered from bronchial carcinoma, began seven months before death to complain of severe shooting pains in his legs. A month later his legs became weak and ataxic. Examination five months before death showed no affection of the cranial nerves nor of intelligence. His arms were weak and he could only walk with assistance owing to extreme ataxia of the legs. His right knee-jerk and both ankle-jerks were absent. Sensation was practically intact. The cerebrospinal fluid contained a great excess of lymphocytes and of protein with a negative Wassermann reaction. He went rapidly downhill, becoming helpless and demented. The plantar reflexes became extensor in type, but there was no loss of skin sensibility and no nystagmus.

Post-mortem examination showed well-established degeneration of the dorsal spino-cerebellar tracts with earlier degeneration in the ventral spino-cerebellar and pyramidal tracts and the dorsal columns. There was great loss of Purkinje cells in the cerebellum with preservation of granule cells and cortical nerve-fibres. The left dentate nucleus and superior cerebellar peduncle were the seat of well-established degeneration. Both nuclei of Luys and the strio-Luysial fibres were degenerated, and there was also slighter degeneration of the right superior cerebellar peduncle, both fillets and the lower half of the posterior longitudinal bundle. This degeneration was everywhere associated with intense perivascular infiltration.

DISCUSSION.

(a) *Relationship to other Forms of Cerebellar Degeneration.*

These two cases of subacute spino-cerebellar degeneration differ in several ways from the cases of cerebellar degeneration which have previously been described. Of those with an onset in middle or advanced life there are two main groups: (1) *Parenchymatous cortical cerebellar atrophy*; and (2) *olivo-ponto-cerebellar atrophy*. Subacute spino-cerebellar degeneration differs from parenchymatous cortical atrophy on the clinical side in its onset with pain and paræsthesia in the limbs (paralleled only by Rossi's Case 3), its rapid course and its association with mental deterioration. On the anatomical side the cerebellar lesion is similar. In both types there is loss of Purkinje cells with relative preservation of the granules, basket cells and white matter of the foliæ and little shrinkage of the cerebellum as a whole. The chief distinction lies in the degeneration of the spinal kinetic system, that is of those tracts which convey kinæsthetic impressions, as well as of the pyramidal tracts. In addition there was in both our cases degeneration of the nucleus of Luys and of the strio-Luysial fibres.

The distinction from olivo-ponto-cerebellar degeneration is more fundamental, although here, also, there are many common features. It is doubtful whether any clinical distinction is possible. The course of the illness in Case 1 is, perhaps, more rapid than has been described in olivo-ponto-cerebellar atrophy, but Schroeder and Kirschbaum have described cases of somewhat similar nature which ran their course in six and ten months respectively. Mathieu and Bertrand point out that mental symptoms are not uncommon in the more acute cases of this type of cerebellar degeneration. The distinction therefore is mainly in the incidence of the disease on the cerebellar connections. In olivo-ponto-cerebellar degeneration the primary attack appears to be on the

inferior olive and the nuclei pontis. Van Bogaert and Bertrand have indeed described a case in which these nuclei were atrophied without any evident degeneration of the cerebellum. There are, however, exceptions to this rule. In the case published by Lejonne and Lhermitte under the name *olivo-rubro-cerebellar atrophy* the superior peduncles and red nuclei were affected, the pontine nuclei and middle peduncle being intact. In Schroeder and Kirschbaum's second and third cases the olives were severely degenerated with little or no degeneration of the pontine nuclei or middle peduncles, and the dentate nuclei were involved in both cases. We seem, therefore, to have a group of conditions which while approximating to the type described by Dejerine and Thomas may differ from it in several particulars. It is, however, impossible to include our cases in this group as no degeneration either of the inferior olives or of the pontine nuclei could be made out in them even by Marchi staining.

Degeneration of the long tracts of the spinal cord has been described in several cases of olivo-ponto-cerebellar atrophy. The dorsal columns and spino-cerebellar tracts and the pyramidal tracts in the lumbar region were affected in one of Thomas's cases, and the dorsal spino-cerebellar tracts in a case of Schroeder and Kirschbaum's. Less systematized spinal degeneration has been described by other authors. Our cases differ from these chiefly in the severity and extent of the degeneration in the spinal tracts, the onset of which appeared to be contemporary with the earliest clinical symptoms. The difference here is therefore one of degree rather than of type. But in our cases the spinal degeneration was so well established that it seemed to justify the term "spino-cerebellar" which we have used to describe them.

The most striking new feature in our cases is the degeneration of the nucleus of Luys and of the strio-Luysian fibres. Degeneration of this nucleus is a rare phenomenon. In vascular disease it is more often the site of hæmorrhage than of ischæmic lesions, as it is richly supplied both by the anterior choroidal and the posterior cerebral arteries. Its degeneration in icterus gravis neonatorum (Kernicterus) has been described (Hawksley and Lightwood), and it may be involved in system diseases of the basal ganglia. But that it should be so selectively implicated in a spino-cerebellar degeneration was unexpected. Seeing, however, that olivo-cerebellar degenerations may involve the nucleus ruber (Lejonne and Lhermitte) and the substantia nigra (Ley) the degeneration of the subthalamic nucleus in our cases is not very surprising. It was, however, surprising to find in both cases that the

degeneration was most severe in the outer part of the nucleus and that the "strio-Luysial" fibres passing across the crus were more affected than the bundles of fibres which reach the nucleus at its inner and outer poles. Our knowledge of the anatomical connections of this nucleus is far from being complete, but it appears that the commissural fibres come more from the inner part of the nucleus and the fibres which descend in the stratum intermedium from the outer part.

(b) *Perivascular Infiltration and Inflammatory Nodules.*

A clinical feature of these cases which gave rise to some confusion was the excess of cells and inflammatory changes in the cerebrospinal fluid. In Case 1 the association of such changes with a parietic type of colloidal gold curve made the diagnosis of disseminated sclerosis the most probable one. In fact it was the interest aroused by the apparent onset of disseminated sclerosis at the age of 66, which led to the post-mortem examination being made. In Case 2 also this diagnosis was at one time considered possible, but it was negatived by the high protein found in the cerebrospinal fluid on the first examination. Thereafter no diagnosis could be arrived at which appeared to fit in with the facts of the case. These abnormalities in the cerebrospinal fluid were certainly a reflection of the intense perivascular infiltration which was found on histological examination. The fact that these infiltrations occurred in areas where degeneration was proceeding and not elsewhere made us consider them "symptomatic" in Spielmeyer's sense. That is to say they were thought to be caused by the degeneration of cells and tracts and not to be evidence of infection by a microbe or virus. Ley accepts this explanation for a similar infiltration which he found in the pons in his case of olivo-ponto-cerebellar atrophy.

There is to-day little doubt that such inflammatory reactions may follow non-microbial degenerations. Many well-established observations in general pathology prove this. In particular the zone of polymorphonuclear leucocytes which is seen round infarctions in the kidney and in the brain shows that the presence of necrotic tissue may stimulate the migration of inflammatory cells. It has been suggested that this reaction is greatest in organs containing a large percentage of lipid, such as the liver, the kidney and the brain. Winkelman and Davison have stated that the cells collecting in the perivascular sheaths in tract degenerations always contain lipid, but there seems to be little justification for this assumption. Plasma cells as well as polymorphonuclear cells may be found near a cerebral hæmorrhage or a degenerating

cerebral tumour and the dense cuffs of lymphocytes which are found round the neighbouring vessels include very few fat-containing cells.

In several of the recorded cases of olivo-ponto-cerebellar atrophy the patients were syphilitic, and it was considered likely that this infection bore some ætiological relationship to the disease. The case published by Bielschowsky and Hirschfeld is remarkable in this connection. Here the changes in the cerebellum and brain-stem were those of olivo-ponto-cerebellar degeneration with severe degeneration also in the red nucleus, while those in the cerebral cortex and basal ganglia were considered typical of general paralysis. In this case the pupils reacted to light, and the cerebrospinal fluid, examined a few days before death, gave a negative Wassermann reaction. The diagnosis, therefore, rested altogether on the histological examination and especially on the presence of iron-containing microglial cells in the cerebral and cerebellar cortex. The case has otherwise many points of similarity to those which have already been discussed. The early degeneration in the pyramidal tracts and dorsal columns, and the widespread perivascular and meningeal infiltrations and glia rosettes ally it to those we have described, while the degeneration of nerve cells in the cerebral cortex resembles that found by Schroeder and Kirschbaum. This case reopens the question of a possible syphilitic ætiology for progressive cerebellar degenerations, especially for those of the olivo-ponto-cerebellar type, an ætiology which has been discounted in the more recent literature. At the same time we found no reason to suspect syphilitic infection in our cases and the serological reactions in both were against this possibility.

Nor does it seem to us that these cases support the theory suggested recently by Parker and Kernohan that the more rapid cerebellar degenerations may be due to infection by a virus such as that of "louping-ill." The vulnerability of the Purkinje cells of the monkey's cerebellum to the virus of "louping-ill" does not prove that the human cerebellum is equally susceptible to this virus. Indeed, the clinical course of the disease, as it has occurred in laboratory workers, has given no evidence of this. While it is possible that subacute nervous diseases may be due to a slowly acting virus, there is no positive evidence at present that any virus can act in this manner. The theory that the later manifestations of encephalitis lethargica are due to the continued action of the virus which caused the initial attack, although widely held, has no scientific proof. There is, however, evidence that the virus of poliomyelitis may be recovered from the nervous tissues some

weeks after it has produced its maximal effects ; and it is possible that it may continue there for longer periods and be the cause of the progressive muscular atrophy which sometimes comes on in later life in the subjects of poliomyelitis.

In general the cerebellar degenerations appear to be too well systematized to be the result of virus infection, and in the present state of our knowledge we can do no more than place them among the system diseases of unknown ætiology. Their relationship to Friedreich's ataxia is shown, not only by the anatomical distribution of the lesions and the occasional familial incidence of all forms, but also by the tendency for the tracts to degenerate from the distal end towards the cell of origin, so that the latter is often the last part of the neuron to disappear. In our cases this was observed in the pyramidal tracts and in the spino-cerebellar tracts. This tendency has been equally evident in some cases of olivo-ponto-cerebellar atrophy, and such lesions as degeneration of the fronto-pontine fibres limited to their termination in the pons and of the pyramidal tracts limited to the lower thoracic and lumbar segments of the cord have been described.

SUMMARY.

Two cases of spino-cerebellar degeneration are described. The disease came on in patients aged 66 and 57 years and ran a rapid course, with a fatal termination in three and seven months respectively from the onset of the first symptoms. In both patients pains in the limbs were a prominent early symptom ; this was succeeded by weakness and ataxia of the legs and arms, dysarthria and mental enfeeblement. Nystagmus was indefinite or quite absent and no loss of skin sensibility was found. There was considerable pleocytosis and excess of protein in the cerebrospinal fluid in both cases.

Pathologically the condition was characterized by degeneration of the long tracts of the cord, especially the dorsal columns and cerebellar tracts, with earlier degeneration of the pyramidal tracts. There was gross loss of Purkinje cells in the cerebellar cortex, the granule cells being relatively spared. The superior cerebellar peduncles and the longer tracts in the tegmentum of the brain-stem were involved in the second case. The nucleus of Luys and the strio-Luysian fibres were degenerated in both cases. The substantia nigra, nucleus ruber, nuclei pontis and olivary nuclei were unaffected and the cerebral cortex was intact. In both cases there was fairly intense perivascular infiltration in the neighbourhood of degenerated tracts.

The relationship of these cases to other forms of cerebellar degeneration is discussed.

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LEGENDS FOR ILLUSTRATIONS.

PLATE IX.

Figs. 1 and 5 from *Case 1* should be compared with figs. 2 and 4 from *Case 2*.

FIG. 1.—*Case 1*. 1st lumbar segment of cord. Marchi-Busch method. Degeneration is most evident at this level in the pyramidal tracts and the middle root zone of the dorsal columns.

FIG. 2.—*Case 2*. Upper cervical cord. Weigert-Pal method. Degeneration is seen in the pyramidal and spino-cerebellar tracts and in the middle root zone in the dorsal columns.

FIG. 3.—*Case 1*. Thoracic segment of cord. Hæmatoxylin, van Gieson. To show an "inflammatory nodule" and perivascular infiltration.

FIG. 4.—*Case 2*. Corpus Luysii. Bielschowsky method. There is complete destruction of nerve-cells and overgrowth of neuroglia in this area.

FIG. 5.—*Case 1*. Corpus Luysii. Toluidin Blue. Two fairly healthy and two degenerated nerve-cells are seen in one half of the field. A cell filled with lipoid is present at the opposite corner. Numerous elongated microglial nuclei are present.

FIG. 6.—*Case 2*. Low-power view of ventral part of cerebral peduncle. Marchi-Busch method. The Corpus Luysii and the strio-Luysial fibres passing across the internal capsule stain deeply. The fasciculus thalamicus is less intensely stained.

PLATE X.

FIG. 7.—*Cerebellar cortex in Case 1*. Bielschowsky method. Two baskets are seen in the field. One contains a shrunken and degenerated Purkinje cell. The other is empty. The granules are spaced out a little but there is no loss of tangential or radial nerve-fibres in the molecular layer.

FIG. 8.—*Cerebellar cortex in Case 1*. Anderson's Victoria Blue method. To show thickening of the neuroglial fibres in the molecular layer.

FIG. 9.—*Cerebellar cortex in Case 1*. Toluidin Blue. To illustrate the complete loss of Purkinje cells and the meningeal infiltration.

FIG. 10.—*Cerebellar cortex in Case 2*. Bielschowsky method. No Purkinje cells or dendrites can be seen in this field.

PLATE IX.

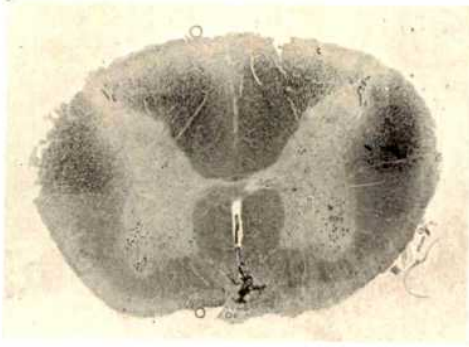


FIG. 1.

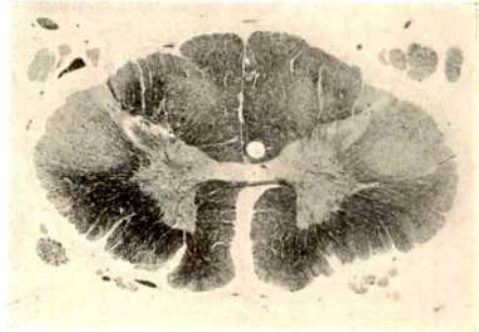


FIG. 2.

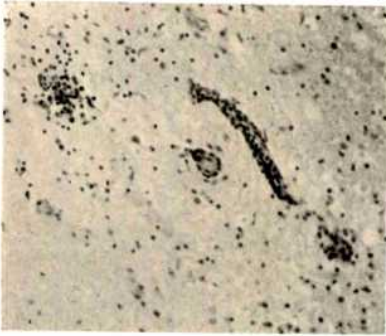


FIG. 3.

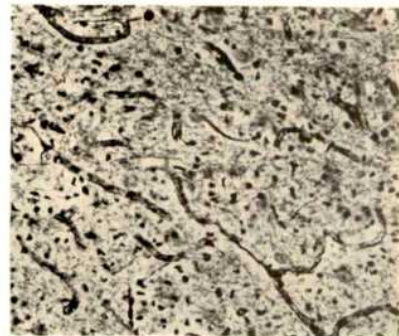


FIG. 4.



FIG. 5.



FIG. 6.

PLATE X.



FIG. 7.



FIG. 8.

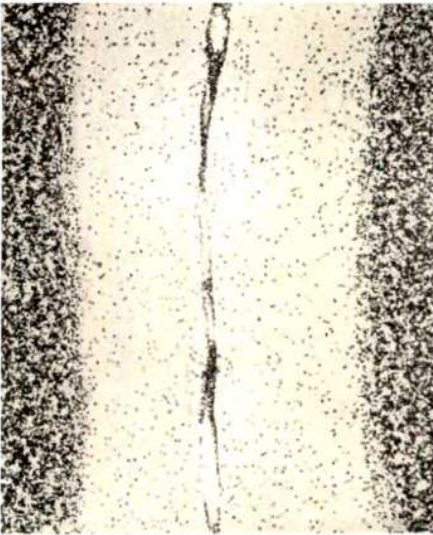


FIG. 9.

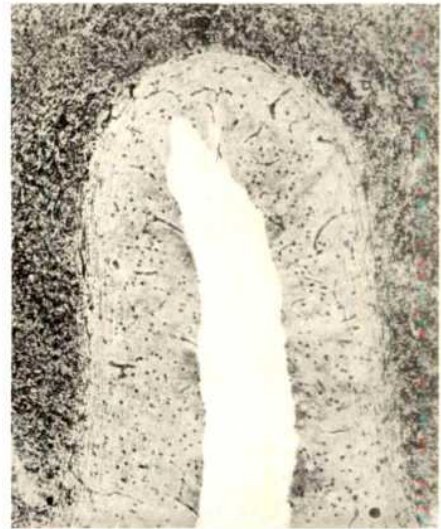


FIG. 10.

To illustrate paper by J. G. Greenfield.

CHOLESTEATOMA OF THE MIDDLE AND POSTERIOR CRANIAL FOSSÆ.

BY G. L. MONTGOMERY AND D. I. C. FINLAYSON.

(From the Pathology Departments of the University of St. Andrews and the Dundee Royal Infirmary.)

CONTEMPORARILY with recent advances in neurosurgery, interest has been reawakened in the intracranial cholesteatomata, the *tumeurs perlées* originally described by Cruveilhier [1]. While many admirable accounts of individual and collected cases have been published, the example here described presents certain unusual features which seem to warrant record.

Clinical history.—C. D., female, aged 19.

The patient was admitted to the Dundee Royal Infirmary in January, 1932, under the care of Professor Adam Patrick, having attended for three months previously as an out-patient. She gave a history of diplopia on looking to the right of twelve months' duration, weakness of the legs on exertion and unsteadiness in walking of four months' duration. Right-sided morning headache occurred four weeks after admission; this was present when the patient awakened in the morning and disappeared in the course of a few hours. There had been no vomiting.

On examination in October, 1931, the patient was a healthy looking girl, clinical signs of disease being confined to the nervous system. There was exaggeration of the tendon reflexes of both arms and legs; the abdominal and plantar reflexes could not be elicited.

There was no muscular weakness and no tremor. The gait was a little unsteady, but there was no Rombergism; there was some ataxia in both arms in the finger-nose test. The pupils were dilated, equal and regular; they reacted normally to light and less briskly on convergence; slight ptosis of the right eyelid and weakness of the right external rectus were present, and diplopia was experienced on looking to the right. There was coarse nystagmus on looking to the right and on looking upwards. Both optic discs showed papilloedema. Vision: right eye $\frac{6}{18}$, left eye $\frac{6}{12}$. Lumbar puncture yielded clear fluid; cells 62 per c.mm. The Wassermann reaction of the blood and cerebrospinal fluid was negative.

On admission to hospital in January 1932, the patient was unable to walk unassisted, and there was a tendency to fall to the right. The patient was not able to stand upright on a narrow base even with the eyes open, always falling

to the right. Papilloedema had increased. V.O.D. now $\frac{6}{36}$, V.O.S. $\frac{6}{18}$. Visual fields show general contracture almost to tubular vision.

The patient was examined on March 3 by Mr. John Anderson, who made a provisional diagnosis of tumour of the right side of the cerebellum. On March 8 he performed a preliminary cerebellar decompression; increased tension of the cerebellar tissue was noted, especially on the right side. A second-stage operation was performed on March 19. The flattening of the cerebellar convolutions had disappeared, but attempts to locate the tumour were unsuccessful. The patient died six days later.

Autopsy.—The thoracic and abdominal viscera showed no important lesion. The bones of the vault of the skull were rather thick. On removing the skull-cap some flattening of the cerebral convolutions was evident, especially on the

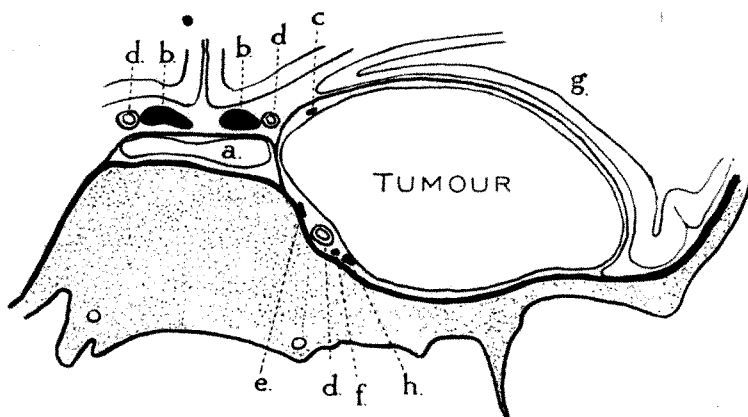


FIG. 1.—A coronal section one inch in front of the auriculo-bregmatic plane to show the relations of the anterior portion of the tumour in the middle fossa. Viewed from behind. (Modified from Macewan's "Atlas of Head Sections.") a, Pituitary body. b, Optic nerve, c, Trochlear nerve. d, Internal carotid artery. e, Oculo-motor nerve. f, Abducens nerve. g, Temporal lobe. h, Second division, trigeminal nerve

right side, and the subarachnoid space was dry. On elevating the right frontal lobe, the right middle fossa was seen to be occupied by a swelling about the size of a golf ball; this lay beneath the dura and proved to be the anterior portion of a tumour of hour-glass shape, which occupied the right middle and posterior fossæ. The soft consistency of the growth, and its dural relationships, necessitated removal in two portions.

The smaller anterior fossa portion of the tumour was pyriform and measured approximately 3 cm. in its longest—transverse—diameter; it extended well forward under the lesser wing of the sphenoid and occupied the medial and anterior part of the fossa. On dissection, this portion of the tumour was found to have a complete sheath of dura mater which separated easily from the true capsule of the tumour, displaying between the dura mater and the tumour the structures normally occupying or entering the cavernous sinus. The fourth nerve pierced the dura mater at the level of the posterior clinoid process and

ran as a flattened band across the supero-medial aspect of the tumour. Medially lay the internal carotid artery with the sixth nerve apparently undamaged immediately below and lateral to the artery. The third nerve lay medial to the tumour and above the artery; it was compressed and flattened in its entire course in the middle fossa; the Gasserian ganglion was separated from the tumour by a reflection of the dura mater; the second division of the fifth nerve was lying below and lateral to the sixth nerve between dura mater and tumour capsule. Fig. 1 is a schematic diagram of an oblique coronal section of the base of the skull cutting the superior surface of the tumour immediately posterior to the anterior clinoid process.

It was clear that the middle fossa portion of the tumour lay between the layers of the dura mater and in fact was occupying the right cavernous

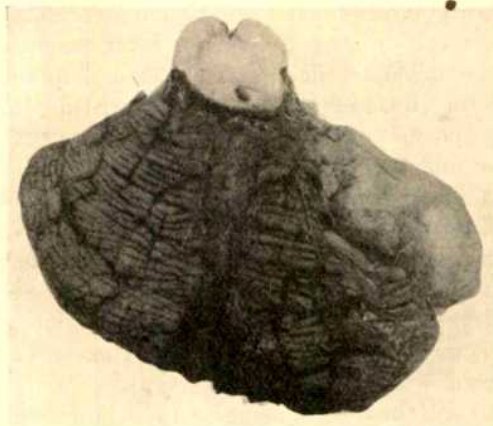


FIG. 2.—Portion of the tumour in the posterior fossa compressing cerebellum.

sinus. The inferior surface of the right temporal lobe was indented and moulded over the portion of the tumour in this fossa, and beneath the tumour the bony floor of the middle fossa was markedly thinned by pressure.

The tumour entered the posterior fossa by a narrow neck which overlay the apex of the petrous temporal bone and became intradural by passing through a well-defined oval aperture in the dura mater which measured 13 mm. in its longer (horizontal) axis, and covered the suture between the petrous temporal and basi-occipital bones. The fourth nerve passed over the neck of the tumour, and the sixth nerve lay medial and inferior to it. The aperture was situated in the posterior wall of the cavernous sinus slightly medial to the exits of the petrosal sinuses. It was completely filled by the neck of the tumour, and in this situation the dura was firmly adherent to the capsule of the tumour.

The portion of the tumour in the posterior fossa (fig. 2) was intradural and was partly ensheathed in an invagination of pia arachnoid; the pearly lustre of the tumour capsule was very evident in this situation. The right cerebellar

hemisphere was much compressed anteroposteriorly. In the incisura tentorii the mid-brain was slightly deviated to the left. The fifth, seventh and eighth nerves crossed laterally beneath the neck of the cyst, but were not in any way damaged. The internal auditory meatus was of normal size, and there was no connection between the tumour and the interior of the petrous temporal bone.

The interior of the growth was filled with semi-solid pultaceous material, consisting of glistening flakes aggregated into small masses.

Histological examination.—The cyst wall proper consists of an epithelial layer supported by a thin fibrous layer, the appearance resembling an inversion of the dermis, i.e. the innermost layer consists of flattened desquamated cells whose nuclei have disappeared, covered by a stratum corresponding to the rete Malpighii. This latter layer has a minimal thickness of from four to six cells which are connected by intercellular bridges, and it presents well-marked rete pegs. In the inner cells of the Malpighian layer granules of keratohyaline are evident, but we failed to demonstrate eleidin granules. The investing membrane consists of an outer more fibrous layer in which lie sebaceous glands and an inner portion of looser texture, projecting between the rete pegs like dermal papillæ and carrying with it infrequent, small, but well-formed blood-vessels. Fig. 3 shows the very close apposition between the dura mater and the wall of the cyst.

In the posterior fossa the cyst wall is thinner (figs. 4 and 5), the epithelial layer having a maximum thickness of only three or four cells supported by a very thin fibrous layer. Prickle cells and keratohyaline granules are again evident, but there is no suggestion of rete pegs. There are no sebaceous glands in the parts examined.

The cyst is filled with cast-off squames. In paraffin sections these do not present the appearance of vegetable cells; the so-called stratum cellulosum, though this appearance was well demonstrated in preparations made immediately after autopsy by Terry's method. In the interior the squames are mingled with cholesterol crystals and other fatty materials, some of which are doubly refracting. Cholesterol was readily recovered from an alcoholic extract of the cyst contents. In the anterior portion of the tumour we found traces of what were certainly hair-follicles, though of an underdeveloped and abortive type. No hair-follicles were found in the posterior portion.

SITE OF ORIGIN.

Owing to the peculiar dural relationships of this tumour the problem of the site of origin was rather puzzling. The portion in the middle fossa lay between the layers of the dura mater and thus occupied and distended the spongy tissue of the cavernous sinus. The foramen surrounding the neck of the tumour was clearly defined with well-formed thickened edges to which the fibrous layer of the neck was firmly

adherent; it did not appear to be a recent accident, but rather a defect of congenital origin through which or from which the tumour had grown. The following hypothesis, based on the supposition that the foramen was the site of origin, appears to satisfy the clinical and pathological findings.

The foramen is situated just medial to the apex of the petrous temporal bone and in this situation the ectoderm from which the inner ear develops comes at an early stage of development (2 to 3 mm. embryo) into close relationship with the hind-brain, just over the first post-oral visceral cleft. Thus, prior to being enclosed in the sclerotomic mesenchyme of the petrous temporal bone, surface ectoderm is separated from neural tissue only by the ganglionic rudiment of the auditory nerve. Such an anatomical arrangement provides a favourable opportunity for an ectodermal rest to be included in the mesoderm at a site approximately corresponding to the posterior end of the cavernous sinus. If the misplaced surface ectodermal cells survive and continue to grow at a normal rate, a mass of cells will form of which the outer cells in contact with the nourishing vessels will assume the character of the Malpighian layer, while the inner cells, deprived of nourishment, will undergo the normal transformation into flattened squames. Such a process occurs frequently in adult life in the formation of implantation cysts of the skin.

It has been shown that in the middle fossa there was only one layer of dura mater above the tumour and one layer below; therefore it is clear that there was not an invagination of the dura mater into the cavernous sinus, but an actual growth into the sinus, from or through its wall. The cyst seems to have grown in two directions from its point of origin, forwards between the two layers of dura mater into the cavernous sinus and backwards (intradurally) into the posterior fossa, so producing an hour-glass or dumb-bell-shaped tumour. The clinical history also suggests that the growth was bipolar from a common point in the region of the dural aperture, and from the data it appears legitimate to conclude that such was the site of the ectodermal inclusion.

NATURE OF TUMOUR.

It will be appreciated from the account of the histology and from the photomicrographs that the wall of the tumour differed in complexity in the two fossæ. In the middle fossa portion the wall represented the structure of dermis and sebaceous glands were readily found in all sections. In the posterior fossa portion no sebaceous glands were found

and the wall was less complex and corresponded rather to epidermis. It would therefore appear that the anterior portion could justifiably be called a "dermoid" cyst, whereas the posterior portion, with its pial attachment, conforms to the "pial epidermoid" of Bostroem [3].

This difference in structure in the two portions of the wall is interesting, not only with regard to nomenclature, but also in relation to development. Clearly if two portions of the wall of a single tumour can differ in structure in this manner, there can be no sharp line of demarcation between intracranial "epidermoids" and "dermoids," a point much discussed by the older writers. This is in agreement with the view expressed by Critchley and Ferguson [4]. The anterior portion of this tumour is the more highly developed, the relatively unopposed and apparently more rapid growth of the posterior portion being probably responsible for the simpler structure of its wall.

Although the cholesteatomata are the least frequent of intracranial tumours, there is on record one case (Bailey, 1924) [5] where the growth involved two cranial fossæ. This was an example in a male, aged 40, who was operated on by Cushing. The major portion of this tumour lay in the left middle fossa with a subtentorial prolongation and a suprasellar projection into the third ventricle. It is probable that the tumour arose in the middle fossa in which its larger portion lay; it was wholly intradural. It bears only a partial resemblance to the case recorded here and we have been unable to discover in the literature any record of a similar case of cholesteatoma which had involved the cavernous sinus.

SUMMARY.

(1) A case of intracranial cholesteatoma is presented which occupied both middle and posterior fossæ on the right side. The clinical history and pathological anatomy are described.

(2) An hypothesis is given accounting for its site of origin and subsequent growth.

(3) Evidence is presented against the view that intracranial "dermoids" and "epidermoids" are to be regarded as separate entities.

We desire to acknowledge our indebtedness to Professor John Anderson and Professor Adam Patrick for permission to publish this and utilize their case records. The microphotographs are by Mr. T. Hamilton, the Laboratory of the Royal College of Physicians, Edinburgh, to whom our thanks are offered.

PLATE XI.

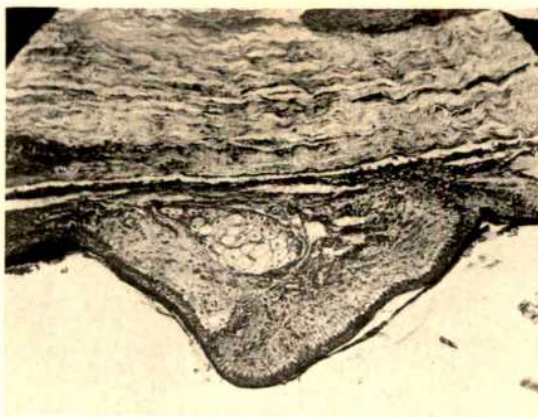


FIG. 3.

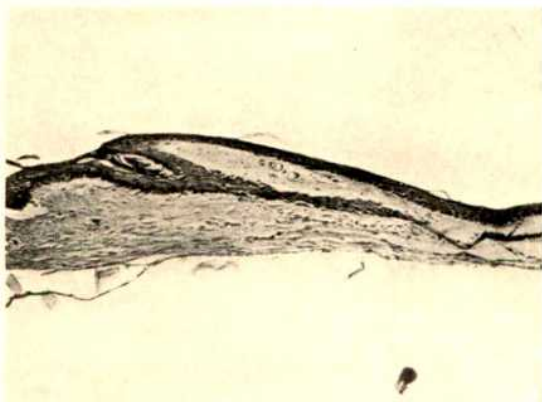


FIG. 4.

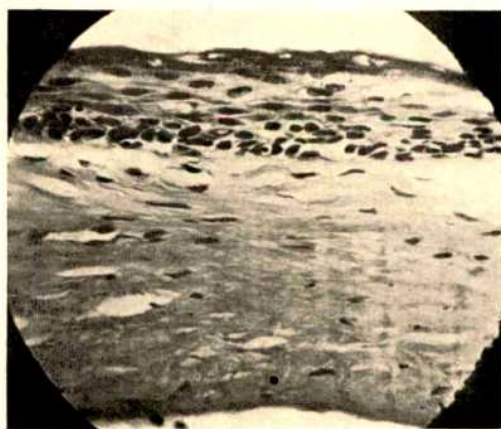


FIG. 5.

To illustrate paper by G. L. Montgomery and D. I. C. Finlayson.

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- [3] BOSTROEM, E. *Centr. f. allg. Path. u. path. Anat.*, 1897, **8**, 1.
- [4] CRITCHLEY, M., and FERGUSON, F. R. *Brain*, **51**, 384-384.
- [5] BAILEY, P. *Arch. Surg.*, 1924, **8**, 524.

DESCRIPTION OF PLATE.

FIG. 3.—Section of cyst-wall from the anterior fossa, showing a sebaceous gland from the cyst-wall and close apposition of dura mater. H × E. × 60.

FIG. 4.—Cyst-wall in posterior fossa. Masson's trichrome stain. × 60.

FIG. 5.—High-power photograph of cyst-wall in posterior fossa to show granules of keratohyaline and prickly-cells. Masson's trichrome stain. × 250.

THE MYOTONIA ACQUISITA IN RELATION TO THE POSTNEURITIC MUSCULAR HYPERTROPHIES.

BY KNUD H. KRABBE,
Copenhagen.

(From the Department of Neurology, Kommunehospitalet, Copenhagen, Denmark.)

It is not rare to find that what are originally described as two "diseases" prove ultimately to be but variants of a single disease. Hepato-lenticular degeneration, first recorded separately as Westphal's pseudosclerosis, and as Wilson's disease, provides a case in point. This is the case, also, of the so-called myotonia acquisita and some forms of true muscular hypertrophy. These have been generally regarded as distinct, although it is known that one may appear as a symptom of the other.

Myotonia acquisita was described originally by Talma [54] in 1892. It bears some resemblance to myotonia congenita, Thomsen's disease, but its origin and course are very different. In both there is marked hypertrophy of muscles and a certain slowness of movement, especially in the passage from fixation to free movement, though once the latter is begun it is rapid enough. The difference between the two maladies is that while Thomsen's disease is hereditary and congenital and progresses slowly during childhood to become stationary in adult life, Talma's disease is not hereditary, but develops acutely after an infection or intoxication and shows after some time a tendency to improvement or to recovery.

In both maladies the symptoms and the topography are the same, yet in their origin they differ as widely as do the muscular atrophies of poliomyelitis and those of progressive muscular atrophy.

The following is a personally observed example of myotonia acquisita.

The patient was a man, aged 24. (Neurological Department, Kommunehospitalet, Copenhagen, 1932.)

He had had tetanus at the age of 12 but had been otherwise healthy until two years before admission to hospital. The tetanus had probably arisen in a traumatic ulcer on the foot where a sinus still remained. The family history was negative.

Three years before coming under observation he had had an acute illness accompanied by severe pain in back and limbs and some weakness of the limbs. Subsequently he had become sallow in colour and developed a progressive tiredness of the arms and hands. Later, rapid movements became difficult, especially extension of the flexed fingers and repetitive movements. He was able to maintain postures and to carry heavy objects.

For some six months a weakness of the legs had appeared and some difficulty in going upstairs. Speech became slower and articulation difficult. These symptoms increased during the winter months. He felt well in bodily health but was somewhat depressed.

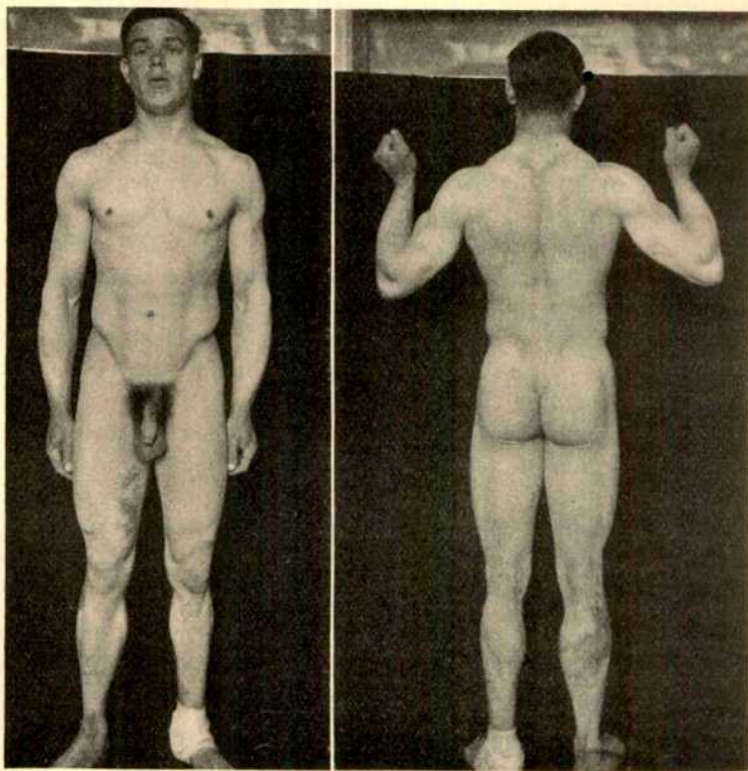


FIG. 1.

On examination: pupillary and ocular movements were normal. A slight hypertrophy of the masseters was the sole abnormality in muscles supplied by cranial nerves.

There was considerable hypertrophy (fig. 1) of the musculature of the neck, back and upper limbs. The lower limb muscles were normal in this respect. The enlarged muscles were firm to palpation but did not show the cotton-like consistency of the muscles of pseudohypertrophic muscular dystrophy. Muscular power was everywhere normal.

After contracting the masseters forty times no fatigue or stiffness developed but movement became slower. All movements tended to be slow. The phenomena of Trousseau and Chvostek were absent.

On electrical examination there was a marked myotonic reaction and diminished faradic and galvanic excitability. The gastrocnemius showed these phenomena most markedly. Cooling the muscles weakened power and diminished faradic excitability. Walking for three hours and injection of 1 c.c. of acetylcholine were without effect upon the myotonic reaction. Erb's phenomenon (wavelike response to galvanism) was not present.

The hirsuties was poorly developed, the skin dry but otherwise normal. The thyroid was not palpable and the testicles were normal.

The cerebrospinal fluid contained $\frac{2}{3}$ cells per cubic millimetre and increased protein content. The Wassermann and Kahn reactions were negative in blood and fluid. The urine was normal. There was achylia gastrica (Ewald's test, performed once). Basal metabolism was 67 per cent. The pulse-rate during test was 44, and one and a half hours after ingestion of peptone, B.M.R. was 75 per cent. and pulse 52. Two hours later B.M.R. 78 per cent., pulse 44. Serum calcium was 10.7 mg. (normal). Serum lactic acid was normal while fasting and after ingestion of galactose. Blood-sugar was 0.079 fasting; a normal response was obtained after galactose. Strauss's concentration test was normal.

Radiograms revealed normal bone formation. The "featherform" appearance of the muscles of pseudohypertrophy was not present. The maximum breadth of the leg was 15.4 cm.

A piece of leg muscle was removed and examined microscopically. No abnormality of any kind was seen, apart from slight increase in the volume of the muscle fibres.

Temperature remained normal while the patient was in hospital. He was given thyroid extract and improved considerably; power and rate of movement increased and the muscles seemed to diminish in bulk.

Analysis of the case shows it to present a myotonic syndrome; slowness of relaxation, myotonic electrical response and true hypertrophy.

The onset was acute at the age of 24, after an illness that may have been a polyneuritis. There was a tendency to improvement. There was no familial element present. The case is therefore one of myotonia acquisita, and it presents all the features described earlier in the literature as typical of that condition.

As mentioned above, muscular hypertrophy is a prominent symptom in myotonia acquisita. Moreover, this symptom may be found as an isolated phenomenon without myotonic symptoms.

The following is a case which I examined recently (June 28, 1933). The patient was a young farmer aged 22. No member of his family (he had seven brothers and sisters) suffered from a similar disease. His parents were not related.

He had been well until the age of 14 to 15, when he contracted a severe angina with fever. He kept his bed for three months, because it was supposed that his heart was affected. During this illness it was observed that his right pupil was dilated, that his face was somewhat asymmetrical and that he had difficulty in closing his right eye. On leaving his bed he was almost unable to walk. After some time the condition of his legs improved but soon got worse again. For the last four years his condition had been stationary. He was inclined to fall. His arms have not been affected. Apart from the weakness of his legs he did not complain of any symptoms: no ataxia, no

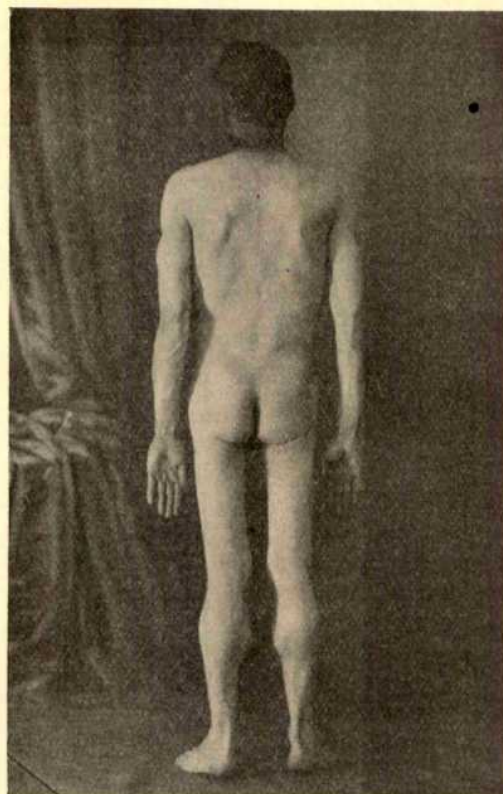


FIG. 2.

pain, headache, giddiness, tiredness, insomnia or loss of memory. Sight and hearing were good and there was no disorder of micturition.

Examination showed the following conditions: ophthalmoscopic examination was normal. The right pupil was considerably larger than the left, but both reacted well to light. His ocular movements were normal, no diplopia existed and no facial paralysis, nor palsy of tongue or palate.

The masseter muscles were somewhat hypertrophied, especially the right one. The lower parts of pectoral muscles were atrophic. The arm muscles

were hypertrophied, especially those of the upper arm. Apart from this, neurological examination of the upper limbs revealed normal power, tonus, coordination, tendon reflexes and sensibility. On palpation the hypertrophied muscles were firmer than normal when they were relaxed, and they were hard as wood when contracted.

The muscles of the back and abdomen were wholly normal. The abdominal reflexes were present. In the lower extremities the gluteal muscles were perhaps slightly atrophied, the femoral muscles very atrophic and the gastrocnemii hypertrophic (fig. 2). Muscular power was fair at the hip-joint, diminished in flexion and especially extension at the knee-joints, but perfectly good at the ankle-joints. Sensibility and coordination were normal. The knee-jerks were very feeble, the ankle-jerks and the plantar responses were normal. Palpation of the gastrocnemii muscles showed the same modification as the hypertrophic muscles of the upper extremities, but less marked. The gait was that of a quadriceps paresis; the patient jerked the legs forward, but did not waddle. When he was lying down and wanted to rise, he supported himself with his hands. All the movements, apart from the gait, were unaffected and without any myotonic character.

Blood-pressure was 120 systolic, 80 diastolic. Urine was normal, and hæmoglobin was 91 per cent.

In connection with this case I should like to give a short abstract of a case which I have published more in detail in 1921.

The patient was 21 years old. There was no history of similar condition in the family. His muscles had always been of normal power. When he was 13 years old he had an illness characterised by pain and weakness of his legs, without fever. For two days he was absolutely unable to walk, but after that the power of his legs improved, but was never completely restored. At the same time his legs became larger and in a short time they reached the volume seen in 1920. On exertion he was soon fatigued and developed pains in his legs, but these symptoms soon decreased on rest. Apart from these symptoms, he felt perfectly well.

The lower limbs presented powerful thigh muscles and enormous hypertrophy of the triceps suræ. On palpation these muscles had not the cotton-like consistency of pseudo-hypertrophic muscles, but that of normal muscles. The power of the gastrocnemii was slightly below normal. The muscles reacted more feebly than normal to the faradic current, but they presented neither the myotonic reaction nor the reaction of degeneration.

Neurological examination of cranial nerves and upper limbs showed no abnormality. General medical examination was negative.

A small piece of the gastrocnemius muscle was excised, and microscopical examination showed that some fibres were increased in volume, some atrophic. In the hypertrophic fibres nuclei were seen scattered in the interior of the fibres, some of which were ramified. Here and there small capillaries were seen entering the interior of the muscle fibres. There was no increase of connective tissue or fat between the muscle fibres, and no sign of inflammation.

If we consider these three cases we find some features common to all of them.

In the first place a muscular hypertrophy, a true hypertrophy very different from the pseudohypertrophy of the progressive myopathies. This muscular hypertrophy had developed in all three cases after an acute illness. In the first case, this was characterized by severe pains in the back, slight pain in the extremities and weakness of the limb muscles. Subsequently a ready fatigue developed in the arms and hands. The second case had a febrile illness and afterwards developed anisocoria, peripheral facial palsy and weakness of the legs. The third case also had an acute illness characterized by pains and palsies of the legs, without fever.

In all three cases, after this initial illness, there developed a true symmetrical hypertrophy of the muscles of the legs or of the arms. In one case the hypertrophy was associated with myotonic symptoms, in the two others no myotonia was observed.

It is generally said that myotonia often presents a muscular hypertrophy as a special symptom. Perhaps it may be more correct to say that muscular hypertrophy presents myotonia as a special symptom. In all the cases it may be supposed that the polyneuritis has caused a certain destruction of the muscles and that subsequently a compensatory hypertrophy has developed.

It has been assumed that myotonia depends upon a hypertrophy of the sarcoplasm. In one of our cases without myotonia, microscopical examination of a piece of muscle showed a hypertrophy of the muscular fibres as a whole. It seems probable that cases in which the muscle fibres in regenerating show such a hypertrophy, a true hypertrophy of the muscles without myotonia results; and that in cases in which the hypertrophy of the sarcoplasm predominates, hypertrophy with myotonia develops.

I have found in the literature thirty-four cases of myotonia acquisita. In all these the patients were males. In the twenty-eight cases in which the age of onset was given this was between 15 and 44 years. However, it must be remarked that cases starting in childhood have not been considered, since it is very difficult to say if these belong to myotonia congenita or myotonia acquisita.

In two cases (Erben, Jeanselme and Huet) the disease developed in patients suffering from pulmonary tuberculosis—a disease sometimes accompanied by polyneuritis. In Schoenborn's case the patient presented an ulceration of the leg, followed by septicæmia. Three years later he

developed a progressive weakness of the arms, and later a myotonia with atrophy. Jacoby's second case developed after an injury to the arms with pain and swelling of the hands. Grund's patient had had long standing ulceration of the left leg, frequently pain in this leg, and his feet became deformed. Later, a myotonia of the hands developed. Beco describes a case in which the patient had an abscess of his right foot. Some time later a myotonia developed of his arm and trunk muscles.

In the case of Huet and Français the patient had been exposed to a torpedo explosion and was completely prostrated. A month later the myotonia began to develop. In Rimbaud and Jourdan's case also the myotonia began after a trauma. Alcoholism has been observed in two cases (Hoffmann, Nartowski), lead-poisoning in one (Haenel). The gastro-enteritic infections play a more important part. Two of Talma's cases developed after severe gastro-enteritis; Bechterew's case, otherwise somewhat atypical, began after an acute gastro-enteritis with vomiting and diarrhoea; in Wexberg's patient the myotonia started in connexion with dysentery, and Jacoby's first case became myotonic, with enormous muscular hypertrophy, after typhoid. However, in the Case 1 of Kornhold the attack of typhoid, which occurred eighteen years before the myotonia, can scarcely be considered as an ætiological factor.

In nine cases (Talma's Case 3, Dercum, Walton, Ballet, Voss, Fuchs, Trömmner, Wagner, Abrahamsen) no ætiological factor is to be found. These cases were adult males without any history of heredity, in whom the myotonic syndrome developed more or less rapidly without any preceding disease.

Finally, in seven cases there were some special features in the onset of the disease. In the Case 1 of Talma, the disease began with weakness of the lower limbs, making it very difficult for the patient to walk. Myotonia developed later. The Case 2 of Talma had, before the myotonia, an acute illness with pains in the extremities, fever and delirium, and later a sensation of heaviness of the limbs. Kornhold's Case 2 began with weakness of the hands, later atrophy appeared, and lastly myotonia. In Jaquemart's second observation, the patient had pains in his right arm, with a sensation of heaviness and weakness, and finally a myotonia (Jaquemart's Case 1 was probably a Parkinsonism).

Salzberger describes a man aged 26, who had been ill three years before the myotonia appeared. This illness consisted in pains in the legs, the arms and the muscles of the chest. In the case described by Beaulieu-Faure and Deschamps the movements of his right arm became feeble, and the feebleness increased slowly.

Rybalkine's patient had an epileptic fit, followed by violent abdominal pain. Eight days later, he noticed that he had difficulty in respiratory movements and in moving the limbs. The first case described by me above belongs to this group.

Finally, it must be noted that in one case only (Fürstner) among these thirty-four, the patient had suffered from syphilis, and this rarity of syphilitic antecedents seems to point to the fact that syphilis does not play any part in ætiology. The fact that the disease very seldom seems to begin after the age of 45, suggests that arteriosclerosis is not an ætiological factor. It is also remarkable that no cases have developed in connexion with disseminated sclerosis or epidemic encephalitis; it indicates that myotonia acquisita is never the result of a spinal or cerebral disease. But if we consider the cases of myotonia acquisita described in the literature, it is significant that most of them developed either after a polyneuritic affection, or after a disease which sometimes causes polyneuritis such as tuberculosis, dysentery, gastro-enteritis, alcoholism, lead-poisoning or traumatic lesions.

The mode of onset of the disease is variable. In most cases it begins with weakness, pain, or flaccid paresis of the limbs, signs which are generally found in polyneuritis.

We will now summarize the cases of true muscular hypertrophy described in the literature, about twenty in all. These were analysed in greater detail in my previous article [35].

In six of these cases (Berger 1 and 2, Lesage, Cerné, Babinski, Bechterew) the muscular hypertrophy developed after typhoid fever. The Case 1 of Curschmann developed after a lead-polyneuritis. Graves' patient developed muscular hypertrophy after sciatica, and Lhermitte's after a traumatic lesion of the sciatic nerve. Popoff's patient had suffered from pleurisy or pneumonia before developing the muscular hypertrophy.

Further, some cases are described (by Krau, Talma, Curschmann (2), Krabbe) in which such polyneuritic symptoms as paraesthesiae, pain and weakness of the muscles, preceded the muscular hypertrophy.

In two cases only (Pal, Woods) hypertrophy seems to have been connected with a cerebral lesion.

The relatively numerous cases developing after typhoid fever have been considered by the authors as due to a phlebitis. If we analyse the history of the disease it seems more probable that the preceding illness had been a neuritis caused by typhoid fever.

On considering these cases as a whole, we observe that true

muscular hypertrophy generally develops after a polyneuritic syndrome, or after a disease often associated with polyneuritis.

The following conclusions may be drawn:—

(1) In the majority of cases a polyneuritis recovers completely, or it leaves a more or less marked atrophy of the affected muscles.

(2) In some cases the recovery is excessive, and the muscles hypertrophy. Sometimes a muscle hypertrophies as a whole, presenting normal power or a slight weakness. In other cases, the sarcoplasm especially hypertrophies, and in these a myotonic condition will be the consequence of the hypertrophy.

If this hypothesis be valid, we may consider myotonia acquisita and true muscular hypertrophy as two variations of the same abnormality: an abnormal regeneration after neuritic processes.

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THE PARTICIPATION OF THE NEUROGLIA IN THE FORMATION OF MYELIN IN THE PRENATAL INFANTILE BRAIN.¹

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INTRODUCTION.

THERE is good presumptive evidence that the oligodendroglia plays an important part in the formation of myelin in the central nervous system. There is still some doubt whether it is the only histological element to participate in this process. Furthermore, the activity of these cells in the development of myelin in the human nervous system has not as yet been carefully studied. For this reason a series of human premature brains were studied in order to trace the activity of all the neuroglial elements in the act of myelin deposit.

REVIEW OF LITERATURE.

Much confusion exists in the literature concerning the histogenesis of myelin. Boll [1] (1869) studied myelin deposit in chick embryos. He found from the eighteenth day of incubation to the first forty-eight hours of post-foetal life a large quantity of dark, fatty-like granules among the axis-cylinders. These granules became confluent and continuous in the form of a sheath. After forty-eight hours of post-foetal life all such fat globules have practically disappeared. Boll thought he could trace the origin of myelin from the fat granular cells which appear in the white substance as early as the seventh day.

Most of the study of myelin formation by cells has been concentrated on the demonstration of fat within cells, it being assumed that fat-containing cells in myelinizing areas were sources of the fat and lipoids constituting the myelin. Jastrowitz [2] (1871) recognized the widespread diffusion of fat in the neuroglia cells during myelin deposit, and

¹ The brains which form the basis of this study were furnished by the Ayer Clinical Laboratory of the Pennsylvania Hospital.

connected them with nerve formation, admitting, however, that the fat in the neuroglia cells might represent the end-products of myelin formation. It was this same appearance which led Virchow [3] to the interpretation that these fat-laden cells were the end-product of degeneration of neuroglia cells. More recently, Wohlwill [4] has asserted that the occurrence of fat droplets in neuroglia is a physiological phenomenon, an assertion which is readily acceptable, but which brings one no closer to the solution of their actual significance. Evidence of a more or less negative nature was produced by Staemmler [5], who studied the brains of dogs and cats in early post-embryonic life. In none of them did he find fat in the neuroglia, whereas in chick embryos he found fat-laden cells with great regularity. Staemmler concluded from these observations that fat in the neuroglia cells in post-embryonic life is pathological, its occurrence meaning that there was a breaking down of myelin, or a disturbed myelin formation with a reversion to an embryonal stage. Its occurrence in rich quantities in the brains of premature infants is accounted for by their being in the embryonal stage of myelinogenesis. Vignal [6] found a close relationship between certain migrating cells, which he called "Hüllzellen," and myelin deposition. These cells, he concluded, were embryonal, migrating from grey to white substance and having the same origin as neuroglia. The nature of these cells is not clear, but presumably they are neuroglial in type. Belloni [7], on the other hand, pointed out a clear relationship between neuroglial development and myelinization in human foetuses of five to nine months. He showed that the fibril prolongations of the neuroglia multiply and form a rete surrounding every single fibre. His conclusion was that if neuroglia cells take part in the construction of myelin, it is seen in the intimate relationship which they form with the myelin sheaths.

That the question of myelin deposit is not a simple process is shown by the important work of Wlassak [8], who incidentally stated that the neuroglia took part in this process. Wlassak believes that the first accumulation of myelin is in the blood, while the first site of deposition is the connective tissue of the pia with which the spongioblasts come into contact with their outer ends. Apparently, the richest deposition is in the spongioblasts situated in the medial plane (Ependymzellen). In lower animals it appears that the property of secreting myelin is a property of the epithelial cells lining the third and fourth ventricles. In them the epithelium lining the roof of the fourth ventricle has the same relation as spongioblasts; the epithelial cells approximating the

blood-vessels contain osmic acid-staining particles in large quantity. The axones in the brain are, with very few exceptions, without sheaths at this early stage, naked axis cylinders being characteristic of all such embryos. Neither fat nor lecithin can be identified round the neuroblasts. As development proceeds, lecithin and fat appear and then later protagon. Protagon first appears in the medulla oblongata of the *Pristiurus* embryo of 30 mm. in the same manner as does lecithin and fat. The characteristic protagon clumps are irregular or rounded in shape, and are sparse in the pial cells. It seems that the accumulation of protagon, lecithin and fat in the animals mentioned depends upon the proximity of blood-vessels. With the ingrowth of blood-vessels into the embryonal brain an entirely new relationship develops. Accompanying such an ingrowth is a constantly diminishing capacity on the part of the ependymal cells to secrete myelin. Myelin is now found more and more about vessels, lecithin and fat being very close to the vessel wall, protagon being at some distance from it. From this time onwards myelin drops and clumps are seen adhering to the myelin-free sheaths and becoming part of them. This transformation can be traced in the embryo of *Scyllium canicula* of 66 mm., and that of *Mustellus lavus* of 2 cm.

Wlassak arrives at the belief that myelin is transported or carried in the form of minute globules from the vessels to developing myelin sheaths. He leaves open the question, but tends to negative the idea, that the basic elements are brought to the axis cylinder, there undergoing a synthetic transformation into a new substance, myelin. Since fat droplets were found to be more numerous in immature than in mature nerve fibres, he thinks there must be a further transformation of fat after reaching the axis cylinder. Fat and lecithin come from the blood in finely divided condition, whereas protagon does not appear in the blood-stream as such. Wlassak thinks that protagon is the result of extravascular synthesis of elemental substances present in the blood.

To the question, "Do tissue cells transport myelin from the blood-vessels to axis cylinders?" Wlassak answers that this transportation is effected by glial cells, definitely in the case of protagon and through inference in the case of fat and lecithin. This latter inference is in contrast with what is seen to occur in the ependymal cells. Here fat and lecithin are found by direct observation, first in the cell protoplasm, and later, in the processes, thus indicating movement in a radical direction.

The first specific identification of the exact type of neuroglia which

takes part in myelinization was made by Hortega [9], who demonstrated the importance of the oligoglia cell in this process. He showed that there are granules present within the oligoglia cell, and that these granules are most abundant during the period of most active myelinization. Shortly after they appear these granules are no longer visible because they have already produced myelin around the nerve fibre. Myelin is a secretion, or rather an elaboration, of the oligoglia. The cells carry to the nerve fibres the trophic materials necessary for the elaboration of myelin. Evidence of the close relationship existing between oligoglia and myelin formation is shown: (1) by the proximity of these cells to the myelin sheaths along which they are placed; (2) by the similarity genetically of oligoglia to the Schwann cells situated along the peripheral nerves; (3) by the abundance of these cells in areas of active myelinization, having been present only in inappreciable numbers, at least before this, and (4) by the increase within the oligoglia cells of granules during myelinization.

He says further that the oligoglia serve as a means of sustenance to the medullary tube, and that its protoplasm elaborates a specific product which influences the trophic function of the nerve fibres and the elaboration of myelin. The clustering of the oligoglia cells along the myelin sheaths in the nervous system has always been suggestive of a relationship of these cells to myelin formation, and the work of Hortega has shown beyond a doubt that the processes of these cells encircle and entwine the medullary tubes of the axis cylinders in the central nervous system. In this respect they are similar to the Schwann cells of the peripheral nerves, a point which was indicated by Cajal and Hortega. The inference has been drawn, therefore, that since the Schwann cells are related to myelin deposit in the peripheral nerves, it seems likely that their analogues in the central nervous system fulfil a similar function.

This view is supported by Penfield [10], and more recently by Morrison [11], who studied the embryos of pigs chiefly, but also of cats, rabbits, rats and humans. He found in the embryo cells which were presumably oligoglia or their forerunners which contained fat, while in the adult this intracellular fat could not be demonstrated. Morrison's demonstration of fat by polarized light served as a definite refinement over the cruder histological methods in use. It has been again supported by Linnell and Tom [12], who found in the white rat of four weeks certain morphological changes in the oligoglia cell, suggestive of the activity of this cell in myelinogenesis. The exact nature of these

changes is not known because the authors have not as yet published their data.

There is good evidence, therefore, that the oligoglia cells and myelin deposit are intimately related. Certainly, in so far as the neuroglia cells are concerned, what evidence there is of their specific participation in myelin deposit points definitely to the oligoglia cells as the important members of this series in this important function.

Material and methods.—All the brains used in this study were human, and all were premature. It was thought that human material was desirable in order partly to correlate what had been observed in lower animals, and partly to determine actually what occurred in myelin

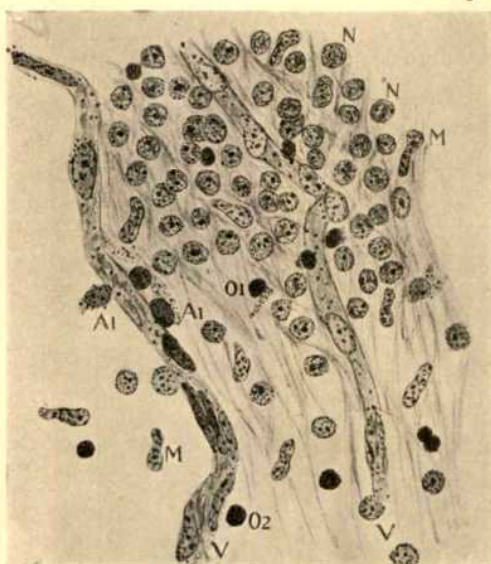


FIG. 1.—Drawing of grey matter of cortex at five-month stage, showing fat globules within vessels, in vascular endothelium, within astrocytes and oligoglia. No fat deposition in axones is found in this stage. Silver carbonate of del Rio-Hortega counterstained with Fett-Ponceau.

formation in the human. Brains were obtained for study from five months till term. Studies on post-natal material were not made because of the inability to get proper material.

The stains employed consisted of the silver carbonate method of del Rio-Hortega, alone and counterstained with Fett-Ponceau, the gold chloride method of Cajal, the osmic acid method of Marchi, Weigert's method and Fett-Ponceau.

The relationship of astrocytes and oligodendroglia to myelinization

in the premature infant brain.—There is strong presumptive evidence from our studies that astrocytes play some sort of rôle in the deposit of myelin before birth. In the Fett-Ponceau stage, globules of fat are seen in the vascular feet in all stages from five months to term. These globules vary in size and are usually round in contour. In the cytoplasm the distribution of fat is usually polar until the ninth month; that is, the fat is concentrated chiefly in one pole of the cell. In the ninth month it becomes more diffusely scattered in the cytoplasm (figs. 1, 2, 3). In the ninth month also, when astrocytes appear to be multiplying very rapidly, the younger astrocytes seem definitely to be

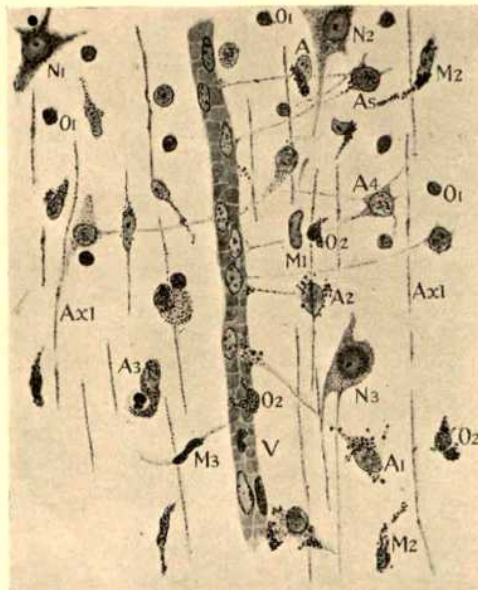


FIG. 2.—Composite drawing of seven-month stage, showing relative abundance of various glial cells. The relationship of fat-laden glia to non-myelinated axones is demonstrated. N₁, N₂, N₃, nerve-cells; A, astrocytes; O, oligodendroglia; M, microglia. Silver carbonate of del Rio-Hortega counterstained with Fett-Ponceau.

more active fat containers than the more mature cells. In Marchi preparations osmic acid granules were found in astrocytes in the seventh and eighth months, but they could not be demonstrated in the ninth month. A rather striking appearance was noted in Weigert preparations (fig. 7). In the ninth month foetus, but not before, blue, globoid bodies could be demonstrated in the cytoplasm of astrocytes, but in no other neuroglial element. These were found in the astrocytes within the cortex and about the axis cylinders in the white matter.

It is important to emphasize that these globoid bodies occur only in the ninth-month foetus, and that they are stained with the Weigert myelin stain only in the axones and the astrocytes. They are not found in the other glial elements. Furthermore, this myelin is of the same colour both in the astrocytes and the axones. It is fair to assume that it is myelin with which we are dealing in this stage because of its staining properties with Weigert's myelin stain. The occurrence of myelin therefore only in the astrocytes and axis cylinders in this stage suggests strongly that these neuroglial elements must play some rôle in myelin deposit. Exactly what this rôle is cannot be defined, but its part cannot be denied.

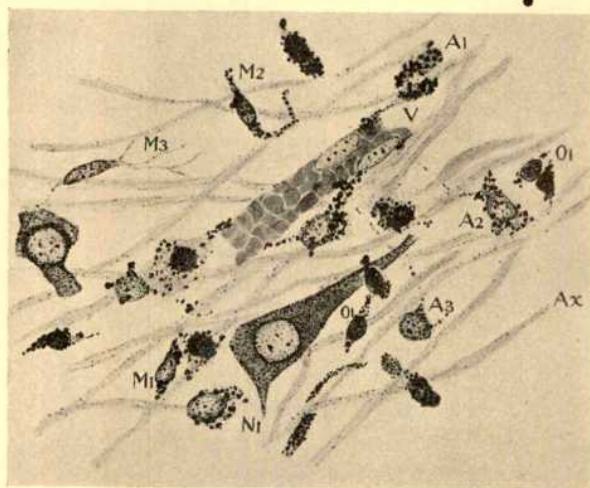


FIG. 3.—Drawing of white matter of cortex of nine-month stage, showing axones now in the stage of active myelin maturation. Fat-laden glial cells are seen in their relative proportions in their relation to these axones. The glial cells now contain the maximum of Fett-Ponceau stained fat. Silver carbonate of del Rio-Hortega counterstained with Fett-Ponceau.

Furthermore, there is the highly suggestive observation made from our sections that osmic acid is found in the astrocytes in the seventh and eighth-month stages, only to disappear suddenly in the ninth month when myelin is found within these cells. This is suggestive of the fact that there is possibly some synthesis of fat into myelin in the astrocytes.

During the sixth to the ninth months of foetal life, fat droplets may be seen in the oligodendroglia cells stained with silver and Fett-Ponceau. In this respect they are similar to the astrocytes. During these stages we were unable to demonstrate any marked predominance in number of

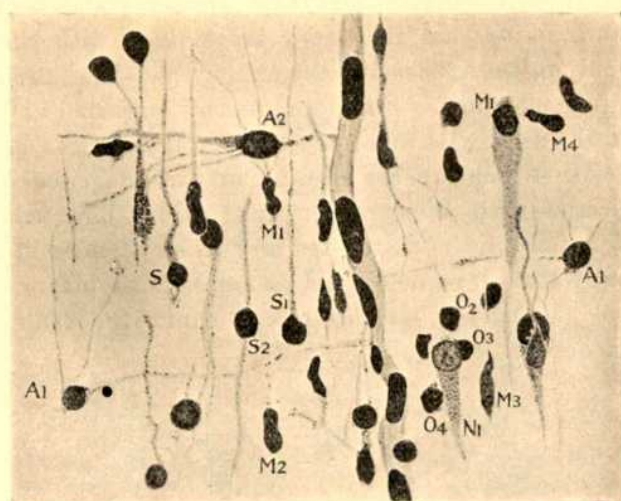


FIG. 4.—Drawing of white matter of cortex of seven-month stage, showing immature glial cells whose dendritic processes are already in close relation to axones. O₂, O₃, O₄, oligoglia grouped about a nerve-cell body. S₁, S₂, S₃, spongioblasts. Silver carbonate of del Rio-Hortega.

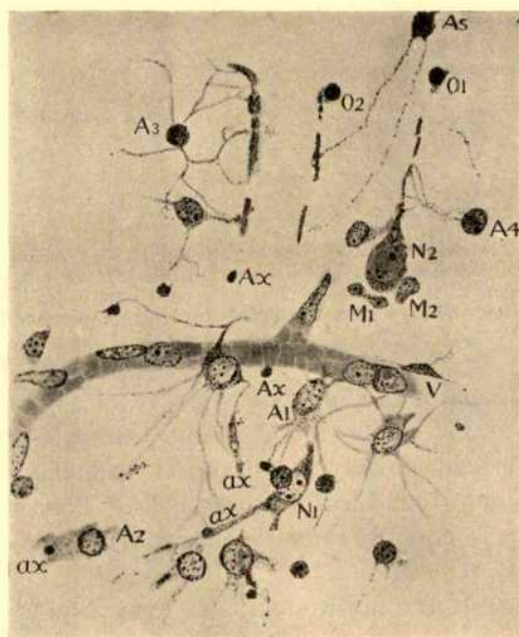


FIG. 5.—Composite drawing showing relationship of astrocytes and oligoglia at the eight-month stage. Note how the astrocytic processes apparently end as a rule at the point of greatest swelling on the segmented axones. Silver carbonate of del Rio-Hortega.

oligodendroglia. While they seemed to be more numerous than the astrocytes, the difference did not appear to be very striking. No globoid bodies were demonstrable in the oligodendroglia with Weigert's stain.

The microglia do not contain fat in the five or six-month stages, but from the seventh month on they contain an increasing amount of fatty substance.

During the fifth, sixth and seventh-month stages, there is an abundance of fatty globules within the vessels, particularly in the cortex.

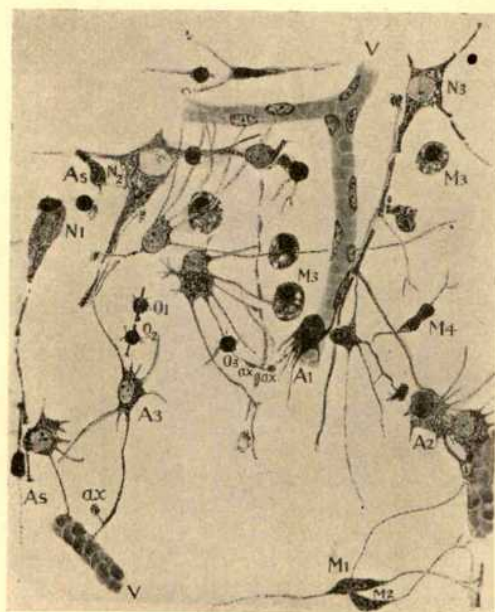


FIG. 6.—Composite drawing showing glia-axonal relationship now at ninth month. Astrocytic communication with axones is most pronounced in this stage. Relatively the astrocyte predominates though all glial elements show proliferation. Silver carbonate of del Rio-Hortega.

Globules are found also in the endothelium of the vessels, but this has disappeared by the eighth month. Fat is not found in the vessels in the ninth month of fetal life.

It is well recognized that the oligodendroglia lie in close intimacy to the axones of the nerve cells in adult life. A similar relationship appears to exist in the embryo between the astrocyte and axone (figs. 4, 5, 6). In both gold chloride and silver preparations it was possible to see astrocytic processes extending to the axone and appearing to terminate there or very close to it. This appeared to be true

particularly of the eighth month stage, where a large number of such processes were seen. A similar relationship is visible in the ninth month foetus. Processes may be seen leading directly to the axone and apparently terminating there; or they may course along an axone and give off fine branches to the latter. The relationship is clear and striking. While its significance is not clear, it would seem to lend support to the idea that the astrocytes play some sort of rôle in the axonal development, possibly in the myelin formation about it.

There is no doubt from the work of Hortega, and more recently of Morrison, that the oligodendroglia play an important rôle in the deposit of myelin. The presumptive evidence for this conclusion stands on firm ground. There is also reason to suppose from our investigations, that

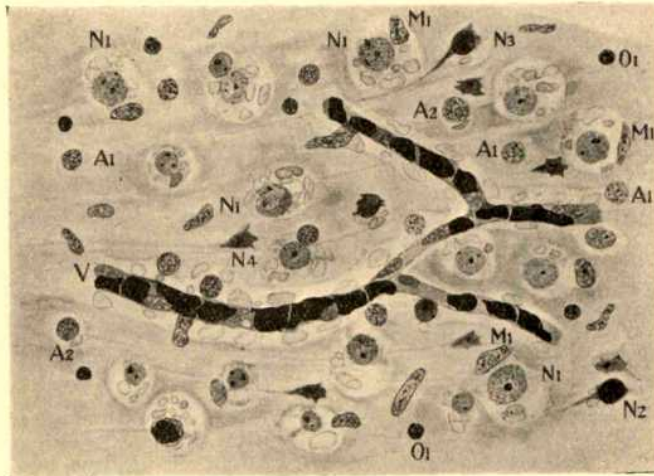


FIG. 7.—Composite drawing of grey matter at nine-month stage, showing globoid bodies in nerve-cell bodies, in astrocytes and in a few oligoglia and microglia cells. Weigert stain.

astrocytes may play a rôle in the premature foetus in myelin formation, for side by side with the fat accumulation in the oligoglia cells there is a similar accumulation in the astrocytes. While it is difficult to judge of the relative abundance of these cell elements, the astrocytes during these stages seem to be as numerous as the oligodendroglia cells. Incidentally, fat was also found in the microglia in the seventh, eighth, and ninth months of foetal life, so that in these months neutral fat is demonstrable in all the neuroglial elements. Just what relationship this presence of fat in microglia has to myelin deposit is very difficult to say, but if it is regarded as evidence of myelin formation in the oligodendroglia, there is no reason to presume that it may not have the

same significance when found in the other neuroglial elements. The presence of fat in the premature microglia was of course well known to Hortega, who however did not commit himself as to its significance. The presence of fat in the astrocytes during myelinization, as seen in our studies, and the intimate morphological relationship of these cells to the developing axone, make it appear probable that the astrocytes play a part in the function of myelin deposit about the axis cylinder. The exact nature of this function, whether it be transportation of fat or some other necessary function in myelin formation, is not clear and remains for future clarification.

CONCLUSIONS.

(1) Premature infant brains ranging in age from five to nine months were studied by means of specific neuroglial methods.

(2) In addition to oligoglial participation in myelin deposit, it was found that astrocytes also played a rôle in this process in the premature brain.

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NOTICES OF RECENT PUBLICATIONS.

Gehirnpathologie: von K. KLEIST. Leipzig: J. A. Barth. 1934.
S. 1068, with 413 illustrations. Price 118 M.

In German, the word "Pathologie" is generally applied to disturbances of function rather than of structure, and this book might be, therefore, titled in English "Symptomatology of the Brain." It, with a smaller part on mental disorders, forms a volume of a series devoted to medical experiences in the War, and it is in fact written around the author's experiences in the treatment of cerebral wounds. It is, however, by no means limited to war-time observations, and these are employed mainly to confirm, elaborate or modify the neurological experiences of ordinary civil life. It deals chiefly with the effects of lesions of the cortex, which is, of course, the part more frequently damaged by wounds.

In a book of this size the reviewer can do scarcely more than point out its scope, the manner in which the subject is dealt with, and the features that distinguish it or add to its value. In the first two sections disturbances of motility and sensation are considered in considerable detail, and they are followed by a long chapter on apraxia, a new form of which is described. The section of visual disturbances includes, in addition to defects in visual perception, affection of colour vision by cerebral lesions, disturbances in visual agnosia, orientation, localization and attention, as well as the abnormalities in reading, writing and dealing with figures which may be associated with lesions of the visual apparatus. The chapter on hearing is concerned mainly with the various forms of amusia. The next 250 pages deal very comprehensively with aphasia, a difficult subject which is not made easier by the manner of its presentation. The symptomatology of the frontal lobes is quite as fully discussed, and many important and some new observations are described. The next 100 pages are concerned with the psychokinetic, catatonic and myostatic disorders associated with disease of the basal ganglia, and a shorter chapter is allotted to disturbances of smell and taste. The remaining pages describe the psychical symptoms which may accompany injury of the brain.

On asking oneself, after reading through these thousand and more pages, what fruit has been born of the author's extraordinary industry, we can in the first place say that a number of interesting facts and observations have been brought together and have been discussed in a manner which will be new and instructive to English readers. On these grounds the book must be strongly recommended for study as well as for reference. A large bibliography, which is almost wholly German, and an index will facilitate its use for the latter

purpose. Yet the reader's feeling is mainly one of disappointment; although numerous small points are studied in detail there is no larger view, no attempt to draw conclusions of a wider application; on the contrary, the tendency is towards over-differentiation, to subdivide each group of observations into smaller entities and leave them isolated.

But the most striking feature of the author's work is his desire to find a precise cerebral localization for every phenomenon he observes. In a series of diagrams of the basal ganglia and the upper part of the brain-stem, for instance, he has marked out the sites of the lesions responsible for not only all the myostatic disturbances, but also for psychokinetic and catatonic symptoms; and on charts of the surface of the brain in the last chapter the localization of various faculties is represented as profusely as ever they were by the most ardent phrenologist.

Neurology. By R. R. GRINKER. Pp. 979. London: Baillière, Tindall and Cox. 1934. Price 38s.

The appearance of each new textbook on neurology brings the question why has it been written? In this instance the answer is offered in the author's preface and by the complimentary notice which accompanies this book, according to which the aim has been to present neurology as a part of the biological sciences applicable on the one hand for the study of disorders of the nervous system by disease, but available also for the student of biology who is interested in the study of other animals. With this object in view the author has devoted his first 100 pages to the embryology, anatomy, physiology and pathology of the nervous system. Some knowledge of these subjects is, of course, essential to the serious student of neurology, but it is very doubtful if they can be properly dealt with within this compass, or by the method of presentation which is adopted here. The pages are too packed with statements, and their arrangement is not always satisfactory. On the second page, for instance, the reader finds presented to him so concisely as to be scarcely intelligible even to one already acquainted with the matter, some of the complicated problems of modern experimental embryology, and the nature of the conduction of nervous impulses, conditioned reflexes and other subjects are so briefly dealt with that the student can be scarcely expected to obtain any useful knowledge from a study of these paragraphs. Less striving after encyclopædic completeness would have produced a more useful introduction to practical neurology.

The sections written from the author's personal knowledge and experience, as those with purely clinical applications, are more satisfactory and in some respects admirable; the classification adopted is probably as good as any classification can be, and the descriptions of symptoms and the discussions on diagnosis are on the whole adequate. The sections on the morbid anatomy and pathology are, however, in many cases incomplete and sometimes so sketchy that the student cannot obtain from them any clear picture of the nature of the disease under discussion.

Unfortunately some sections of the book are marred by a tendency to state opinions and often vague hypotheses as facts, and by a lack of critical selection in the citation of authorities. Later editions would be improved by more careful editing, especially in paragraphing and heading.

There are numerous illustrations, useful references at the end of each chapter, and an index.

Abscess of the Brain. By E. MILLS ATKINSON. Pp. 289. London: Medical Publications, Ltd. 1934. Price 21s.

The author's personal experience of cerebral abscesses has not been extensive, but he has added to it by the study of museum specimens and of the literature. In this volume he states plainly most of the problems and difficulties which the subject presents in practice, but it cannot be claimed that he has added much to our general knowledge of it.

The chapters on the pathology of abscesses and of local cerebral infections, which occupy a considerable part of the book, are the most valuable and interesting; those on diagnosis and localization offer little to anyone with neurological or even general clinical experience, but the views expressed are on the whole sound and safe. In spite of the lamentably high mortality of acute abscesses of the brain exploratory puncture and early operation is recommended, though there is now a good deal of evidence that better results would probably come from a more conservative attitude.

Persons One and Three: a Study in Multiple Personalities. By S. I. FRANZ. Pp. 188. New York and London: McGraw-Hill Book Co., 1933. Price 7s. 6d.

The interest of this small book is that it gives, without hypotheses or psychological explanation, the history over two or three years of a man who was subject to changes in personality, or to periods of continued amnesia, during some of which he was carefully questioned and examined. The author, therefore, provides valuable material for further investigation of the subject. It was found that every change in personality was preceded by a period of emotional strain.

Die parasagittalen Meningeome. von H. OLIVECRONA. S. 144. Leipzig: G. Thieme. 1934. Price 24 M.

The author limits the term parasagittal meningioma to tumours attached to the walls of the longitudinal sinuses or to the falx. For the purpose of clinical description he has divided his own cases into groups according as they lay in the anterior, middle or posterior third of the sinus, and as the symptoms depend largely on the position of the growth, this classification is useful. He estimates the frequency of bilateral tumours, or more correctly the extension of growths through the falx so that they compress both cerebral hemispheres, at one third to one half of all cases, a proportion which is much higher than

it is generally believed to be, but accurate figures can probably not be obtained from operative material. The nature and histology of these tumours is not dealt with, but emphasis is laid on how often they invade the dural veins and sinuses and even lead to their occlusion. This probably plays an important part in the production of the symptoms, which Olivecrona believes are largely due to vascular disturbances, and especially to venous congestion.

This is undoubtedly a valuable monograph which will repay study. Both the text and the illustrations are excellent.

Les Origines du Caractère chez l'Enfant. Par HENRI WALLON.
Paris: Boivin. 1934. Pp. 267. Price 24 fr.

Developmental studies are much in favour in psychology to-day, but have so far added relatively little to our understanding of the adult. This may be due to the use of unfruitful hypothesis, to the complexity of the material, or to the pre-occupation of many observers with morbid phenomena. It is profitable to meet a survey of the field which goes no further than the agreed facts. Dr. Wallon offers an interpretation which necessarily takes the child's own body as the point of departure, and after examining the phenomena of the first three years of life, considers how from these the development of personality can take place. The first part deals with the various aspects of emotion, paying regard, in the last chapter particularly, to the relation between mental activity and muscular tone; in the second part the individualization of the body and awareness of it are considered, and in the third part consciousness of oneself.

A critical period, so far as personality is concerned, is considered to occur at about the age of 3 years.

Psychiatrische Vorlesungen für Ärzte. von KURT SCHNEIDER. Leipzig: Thieme. 1934. S. 140. Price Rm. 3.40.

A simple brief survey of psychiatry for the needs of the general practitioner is offered in these lectures: they contain nothing profound, nothing difficult or controversial, and nothing new for the psychiatric reader. The points made are sensible, and the work, which appeared in a medical weekly, is lucid and may be useful for beginners.

Das Triebverbrechen. von WALTHER RIESER. Bern: Hans Huber. 1933. Pp. 136. Price Rm. 6.80, or fr. 8.50.

This book contains protocols of various criminals and a discussion of the social and personal factors that in these cases provide an explanation of the criminal behaviour. It is unfortunate that the author has not considered how far these illustrate the various ways in which the environment can work upon different constitutions, the understandable connections being but later links in the chain of causality; but he is concerned more with the forensic-psychological approach, and for this purpose his material has the advantage of being

first-hand and full. Some of the forensic sections are directed towards German courts and procedure, but the discussion of responsibility in sexual and other crimes with an emotional background is of interest to all engaged in forensic medicine.

L'Émotion. Par RENÉ DEJEAN. Paris: Alcan. 1933. Pp. 261.
Price 35 fr.

The biological value of emotion is a familiar problem; it may be that in the form in which it is often posited it does not admit of a solution. Dr. Dejean, who has in a previous work concerned himself with reality as it is visually perceived, sets out to discover why such and such an object or situation should provoke the psycho-physiological phenomena of emotion in one person and not in another, how it does so and why these phenomena should be to our disadvantage in that they interfere with our successful adaptation to reality. In his elaboration of these questions he pays much attention to the bodily changes in emotion and to the questions of individual values and of diathesis. His views are interesting but the exposition is much longer than its content seems to warrant, and it adds little to the already available answers to his initial questions.

Les Fous satisfaits. Par PAUL MONDAIN. Paris: Les Éditions Vega. 1933. Pp. 194 (avec 15 dessins originaux de l'auteur).
Price 20 fr.

The author makes no ambitious claims for this work; he professes only to have collected types of gaiety and joy in mental disorder and to have depicted them in words and drawings. The latter, which are in pen and ink and crayon, show his talent, but as is often the case with such illustrations, one would in many instances be unable to recognize the type of disorder from the drawing alone. The verbal descriptions are written in a vivid journalistic style and have some freshness about them. There is of necessity a good deal of psychiatry in the book, but it seems to be written mainly for the untrained reader.

Writers of "Original Articles and Clinical Cases" are supplied free of charge with 50 copies reprinted in the form in which the paper stands in the pages of "Brain." If reprints are required in pamphlet form, with wrapper, title-page, &c., and re-numbered pages, they must be ordered, at the expense of the writers, from Messrs. BALE, SONS & DANIELSSON, Ltd., 83-81, Great Titchfield Street, London, W.

Members of the Neurological Section of the Royal Society of Medicine can obtain the Index of "Brain" for the Volumes I to XXIII inclusive, that is, from its commencement to the end of 1900, from Messrs. MACMILLAN & CO., Ltd., St. Martin's Street, London, W.C., at the price of 8s. 6d., post free.

To those who are not members of the Neurological Section of the Royal Society of Medicine the price is 8s. 6d. net, and the volume may be obtained through any bookseller.

EDITOR.

OCTOBER, 1934.

BRAIN.

PART 3, VOL. 57.

OBSERVATIONS ON REFERRED PAIN.

BY CHARLES BOLTON.

THE observations described in this communication were made with the object of affording evidence that pain and tenderness in patients with gastric and duodenal ulcer is of the visceral referred type, quite apart from the question as to whether splanchnic pain occurs in addition.

Referred pain does not occupy the important position in clinical medicine to which it is entitled, and the theory of the mechanism of its production as laid down by its originators, more especially Mackenzie, has recently been called into question. The older clinical observers recognized it; for Hilton [1], of Guy's Hospital (1863), believed that morbid conditions of the internal viscera were associated with pain situated on the surface of the body; and Martyn [2], of Bristol (1864), considered that the impression of distress in the heart was received through nerves entering the grey posterior columns of the spinal cord and that the central impression was irradiated and referred by the mind to the sensitive skin. Ross [3] (1888) clearly distinguished this referred, or somatic, pain from splanchnic pain conveyed by afferent sympathetic nerves from the organ, which is the origin of the disturbance. But Mackenzie [4] (1892) gave the first objective evidence in favour of this theory, by drawing attention to associated tender areas in the body wall, cutaneous hyperæsthesia and increased reflex muscular irritability. His most important and decisive observation as regards the abdomen was that by which he proved that the tender areas in patients with gastric ulcers occurred in different positions from that of the ulcers. The point of maximum pain corresponded with this tender area. The pain and tenderness were definitely fixed in position, usually in the central line,

whilst the ulcer was found at an operation or post mortem in different positions lateral to this.

It is unnecessary for my purpose to refer to other work on the subject, except that of Morley [5] (1931). Morley claims that Mackenzie's observations are untrue, and that the position of the tender area corresponds with that of the ulcer. His method was as follows: He first marked out on a chart the point of tenderness in different positions of the patient, and found that this tender point shifted with these changes of position. He then administered a barium meal and again marked the tender point by a metal ring on the skin in both the upright and supine positions. Films were exposed in these positions, and on developing them the ring was always found to coincide with, or be very near to, the ulcer; the ulcer moved upwards when the patient lay down and the tenderness moved upwards in correspondence with it. He, therefore, claims that the area of deep tenderness is accurately localized over the ulcer and moves with it, and that this proves "that the tenderness is not produced by a 'reflex' or radiation through the afferent splanchnic fibres, since that hypothetical process could only give rise to a fixed and immobile tenderness, the position of which would be determined, not by the position of the ulcer in relation to the abdominal wall, but by the distribution of those sensory nerves in the abdominal wall which entered the same segment of the cord as received the afferent autonomic nerves from the ulcer." He made observations on other viscera also and concludes that: "referred pain only arises from irritation of nerves which are sensitive to those stimuli which produce pain when applied to the surface of the body." The tenderness over the ulcer is, according to him, felt in the overlying skin and subcutaneous tissue as a reflex in response to stimulation of the parietal peritoneum in contact with the ulcer.

Clearly this new series of observations and the deductions drawn from them call for careful examination, because the physician, who is accustomed to deal with large numbers of cases of gastric pain, can hardly fail to be impressed with the accuracy of Mackenzie's observations, and with the utility of referred pain in clinical diagnosis. Since it has become possible to localize the majority of gastric and duodenal ulcers with the X-rays, and to palpate them during the screen examination, referred pain has unfortunately been heard less of than before. Radiologists are universally agreed that on thus palpating the stomach the ulcer itself may be demonstrated to be tender. It is not within the purview of this communication to discuss the nature of this tenderness

and its relation to splanchnic pain. It is, however, important to draw attention to the method by which it is elicited, which is quite different from the light palpation of the clinician. In order to palpate the ulcer, the radiographer presses the anterior abdominal wall against it, and squeezes it forcibly against the posterior wall of the abdomen; and in doing this he employs considerable pressure. The clinician, on the contrary, in testing the abdominal wall for tenderness palpates it lightly against the elastic resistance of the abdominal contents, having first ascertained whether cutaneous hyperæsthesia or subcutaneous tenderness are present or not.

In the Croonian Lectures (1928) I described the analysis of one thousand cases of gastric pain [6]. 715 of these exhibited pain in single areas, of which 533 were present in the sterno-umbilical region, 452 being situated in the mid-line and 81 at the costal margins. The pain is commonly accompanied by tenderness, which occurs in precisely

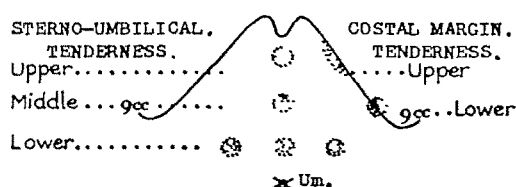


FIG. 1.—To show the areas of pain and tenderness in gastric and duodenal ulcers. Um., the position of the umbilicus. The areas of tenderness in the costal margins are shown in the left side only.

the same area as is painful and corresponds with certain positions on the posterior surface of the body behind. The tender areas, which are constant in position, are most obvious when the pain is at its maximum and they generally outlast the pain. They are present between the individual attacks of recurring pain, finally disappearing more or less slowly when a pain period is ended. A tender point may thus be present without pain; or be present in a different situation than the pain experienced at the same time; or pain may never have been present at the tender spot. Occasionally the painful spot does not become tender. Cutaneous hyper-æsthesia and subcutaneous tenderness are commonly absent; they appear to indicate a higher degree of sensitiveness of the central nervous system than does tenderness of the deeper structures of the abdominal wall. They are particularly liable to occur when the tenderness is diffused beyond the points described, and has affected the whole of one or both sides of the sterno-umbilical

region. Fig. 1 shows the distribution of the tender points in these cases of gastric disease. Most of the points occurred in the central line between the ensiform cartilage and the umbilicus. On this line there are three areas, each about the size of a shilling (2.5 cm.) or larger, namely: (1) At the centre where the transpyloric line joining the right and left 9th costal cartilage cuts it; (2) above this point, just below the ensiform cartilage; and (3) below it near the umbilicus. These three points correspond with the 7th, 8th and 9th thoracic segments, which probably overlap: Head [7], Foerster [8]. There are three further points situated in these segments lateral to the central points just described, namely: (1) in the 9th thoracic segment a few centimetres to the left or right of the central line; (2) in the 8th segment at the costal margin over the right and left 9th costal cartilages, more commonly on the right; (3) in the 7th thoracic segment at the upper portion of the left costal margin, rarely on the right side. The whole central line, or the whole of one or other, or of both costal margins, may be tender; and the tenderness may diffuse over one or other half of the sterno-umbilical region. It will be seen that this description differs from that of Mackenzie in that it includes the lower sterno-umbilical region and the costal margins.

The first and most important objective in the present investigation was to determine definitely the relation of the positions of these tender areas to the positions of the ulcers as seen by the X-rays. The series investigated comprised twenty-five cases of gastric ulcer, thirteen cases of duodenal ulcer, and thirteen cases of painful gastric neurosis. All the cases had been X-rayed and the gastric and duodenal ulcers displayed on the films; all the ulcers were said to be tender to deep pressure. In the cases of neurosis the stomach was proved to be normal by the X-rays and was free from tenderness.

METHOD OF INVESTIGATION.

The tender areas were first determined by light palpation, and marked on the surface of the skin in the upright and supine positions; in every case these two positions were exactly the same. A glass screen, which was specially made for this purpose, was then placed on the front of the body and the outline of the costal margin, the position of the umbilicus and the tender areas were marked on it with a coloured pencil. Radiograms were then taken of the stomach in the supine and erect positions immediately after giving a barium meal, so that the stomach was full; the umbilicus was marked with a piece of metal.

The ulcer, which was found to be tender on screening, was shown in each position of the patient in relation to the mid-line and the umbilicus. The X-ray films were then placed under the glass screen, so that the shadow of the umbilicus on the film and the central line of the spine corresponded with the same positions which had been marked on the glass screen, and the positions in which the ulcer was seen were then marked on the glass screen. The distances of the ulcer from the mid-line, and above or below the umbilicus in the supine and erect positions, were measured in centimetres. By determining the length of the sterno-umbilical and transpyloric lines it was quite a simple matter to draw an accurate diagram, reduced to one-third of the normal size, showing the costal margin, umbilicus and positions of the ulcer, together with the tender areas on the skin. When the glass screen was not available, these measurements were obtained from the abdomen of the patient and the measurements of the positions of the ulcer from the X-ray films. The diagram reduced in size to one-third was then drawn. Either method gives the required result, but with the glass screen the exact shape of the costal margin was more certainly determined. In the supine position the ulcer sometimes disappeared under the costal margin, so that the radiologist could not palpate it to say whether it was tender or not.

RESULTS OF OBSERVATIONS.

The exact positions of the ulcers and the tender points in the abdominal wall are given in Tables I, II, III and IV; and specimen diagrams of the cases are shown in figs. 2 to 9.

GASTRIC ULCER.

I.—*Small Curvature. Twenty-three Cases (Table I).*

Tender areas.—As determined by light palpation the tender areas in all cases except two (22 and 23) were situated in the central sterno-umbilical line. In each case the area involved was about the size of a shilling (2.5 cm.) or a little larger. In nine of the twenty-three cases the tender point was situated in the centre of the sterno-umbilical line; in five it was above the centre near the ensiform; and in two it was below the centre near the umbilicus. In one case (21) all three areas were affected, the whole of the sterno-umbilical line being tender and the tenderness diffused outwards towards the left costal margin; in this case alone were subcutaneous tenderness and cutaneous hyperæsthesia present. In two cases (14 and 18) the middle and lower areas were

combined. In one case the tender point was 3.5 cm. to the left of the lower part of the mid-line; in two it was at the right and in one at the left costal margin. The tender areas on the right side were situated at the 9th costal cartilage, one being associated with a tender area in the upper part of the sterno-umbilical line and the other with tenderness in the middle part. All these points were constant in position, whether the patient stood erect or lay supine. The tenderness might be relieved or increased by contraction of the recti. In the erect position the abdomen may bulge out and increase the length of the sterno-umbilical line, but the tender point in such cases always occupies the same relative position in the line by measurement. These areas correspond exactly with those in fig. 1.

TABLE I.—POSITIONS AS DETERMINED BY X-RAYS OF TWENTY-THREE SMALL CURVATURE GASTRIC ULCERS, AND OF THE TENDER AREAS ON THE SURFACE OF THE ABDOMEN.

No.	Name	Measurements of centre of ulcer to left of midline in cm.		Vertical measurements of centre of ulcer above umbilicus in cm.		Shift upwards in cm.	Tender areas on the surface of the abdomen in the erect and supine positions
		Erect	Supine	Erect	Supine		
1	R. T.	4.5	5	0	8	8	Central line—middle
2	A. W.	1	4	4 (below)	2	6	„ upper
3	S. A.	5.5	6.5	4	8	4	„ middle
4	A. M.	3	3	1	6	5	„ upper
5	O. G.	3.5	1	1	6	5	„ „
6	E. S.	3.5	4.5	3.5	7	3.5	„ middle
7	H. F.	2.5	3.5	7.5	12.5	5	„ „
8	W. D.	5	7.4	0	7.4	7.4	„ „
9	E. D.	3	7	6.5	9.75	3.25	„ lower
10	J. H.	4.5	4.5	8	14	6	„ „
11	W. J.	4.5	0	3	6	3	„ middle
12	E du B.	3.5	4	3	14	11	„ „
13	T. H. G.	4.5	6.5	5	10	5	„ upper
14	P. C. M.	6.5	5.5	5	8	3	„ middle and lower
15	L. G.	4	4.5	7	11	4	„ upper
16	F. B.	4	2	1.5	4	2.5	„ middle
17	T. M.	7	5.5	3	7	4	„ „
18	F. G.	6	5	0	3	3	„ middle and lower
19	H. H.	4.5	6	8	10	2	„ upper and right costal margin 9th c.c.
20	G. M.	4.5	5.5	3	6	3	Central line—middle and 9th right c.c.
21	G. W.	1	3	4.5	4.5	0	Central line—whole and diffusing to left costal margin
22	S. S.	3	4	4.5	8	3.5	Left costal margin upper part
23	A. M.	4	4	3.5	8	4.5	3.5 cm. left of lower part of central line

Position of the Ulcer. Patient Standing.

Horizontal position.—In all twenty-three cases the ulcer was situated to the left of the mid-line, the lateral limits from this position being 1 cm. to 7 cm., and the average 4 cm.

Vertical position.—Three ulcers were level with the umbilicus and one was 4 cm. below it. Nineteen were situated from 1 cm. to 8 cm. above the umbilicus, the average being 4·3 cm.

Patient Supine.

Horizontal position.—One ulcer was situated in the central line. Twenty-two were to the left of this line, the limits being from 1 cm. to 7·4 cm., with an average of 4·6 cm.

Vertical position.—In twenty-two cases the ulcer occupied a higher position than when the patient was standing. The levels varied from 2 cm. to 14 cm. above the umbilicus. One ulcer maintained its vertical position but shifted outwards to the left by 2 cm. In every case except one, therefore, the ulcer shifted upwards when the patient assumed the supine position. The degree of upward shift varied from 2 cm. to 11 cm., the average being 4·7 cm. In fourteen cases the shift was upwards and outwards; in six upwards and inwards, reaching the mid-line in one; in three directly upwards.

In twenty-one cases, therefore, the tender points were situated in quite different positions from those occupied by the ulcer in both the erect and supine positions. These tender points remained in the same position whatever the position of the patient, whereas, in contrast, the ulcers moved upwards in the recumbent position.

These results could not be completely demonstrated in the two remaining cases. For in one (21) the tenderness, which was present from ensiform to umbilicus, extended diffusely leftwards to the costal margin and covered the ulcer in both standing and lying positions; the maximum tender point still, however, remained in the centre of the sterno-umbilical line although the ulcer shifted outwards in the supine position to a point 2 cm. to the left of this point of maximum tenderness. In the other case (11) the ulcer in the erect position was well outside the region of the tender point, but in the recumbent position it moved inwards to the middle line under the tender point which had remained stationary (figs. 2, 3, 4, 5, 6).

II.—Pyloric Vestibule. Two Cases (Table II).

In each case tenderness was said to be present by the radiographer at the cap and pylorus, and a pyloric ulcer was diagnosed.

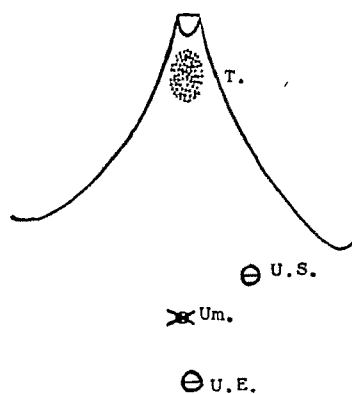


FIG. 2.—Case 2. In this and all the subsequent figures—T., the position of tenderness; U.S., the position of the ulcer when the patient was in the supine position; U.E., position of the ulcer when the patient was standing erect; Um., the umbilicus.

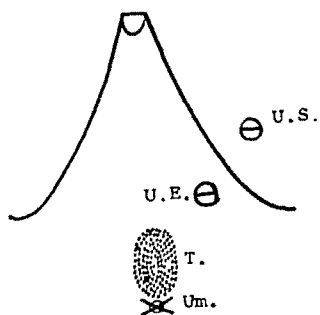


FIG. 3.—Case 9

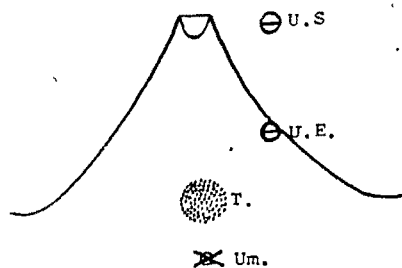


FIG. 4.—Case 10.

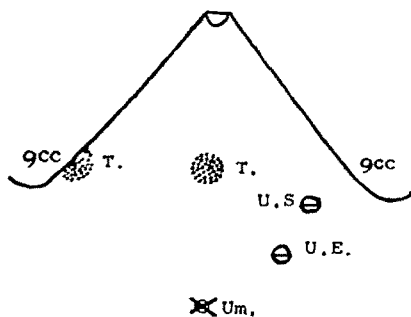


FIG. 5.—Case 20.

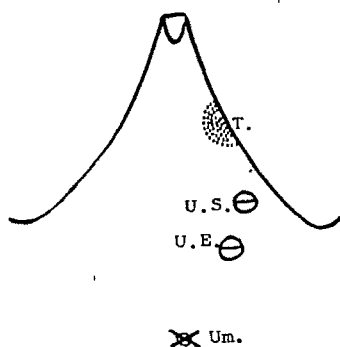


FIG. 6.—Case 22.

One case was inconclusive as far as our present purpose is concerned. There were two tender points of maximum intensity, one at the 9th right costal cartilage and another in the middle of the sterno-umbilical line, but diffuse tenderness extended between this line and the right costal surface, and there were subcutaneous tenderness' and

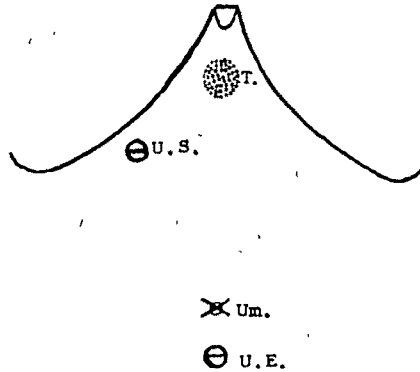


FIG. 7.—Case 24.

hyperæsthesia of the skin also over this area; both in the erect and supine positions the ulcer was situated under this area, its shift upwards being 3 cm. However, its position corresponded neither in the erect nor the supine positions with either of the above maximum points of tenderness, which remained stationary in all positions of the patient.

The other case was decisive, for the tender point on the abdominal wall, which was constant in all positions, was situated in the upper sterno-umbilical line below the ensiform, while in the erect position the ulcer was situated in the mid-line 3 cm. below the umbilicus, and in the supine position it had shifted upwards and outwards for a distance of 9 cm., to a point 5 cm. to the right of the central line (fig. 7).

TABLE II.—POSITIONS OF TWO PYLORIC ULCERS AS DETERMINED BY X-RAYS, AND OF THE TENDER AREAS ON THE SURFACE OF THE ABDOMEN OBTAINED BY LIGHT PALPATION.

No.	Name	Measurements to right of mid-line in cm.		Vertical measurements above umbilicus in cm.		Shift upwards in cm.	Tender areas on the surface of the abdomen, in the erect and supine positions
		Erect	Supine	Erect	Supine		
24	B. W.	0	5	8	9	12	Central line—upper
25	J. W. C.	7.5	7.5	below 9	12	3	Central line—middle; and right costal margin 9 c.c., and diffusely extending to whole of right sterno-umbilicus region

DUODENAL ULCER.

Thirteen Cases (Table III).

In all these cases the duodenal cap was reported to be deformed and tender.

Tender areas.—The tender areas were situated in the central sterno-umbilical line in eleven cases, the size of the areas being the same as in the cases of gastric ulcer. In four cases the tenderness was situated in the middle of this line; in four in the upper part below the ensiform; in

TABLE III.—POSITIONS OF THIRTEEN DUODENAL ULCERS AS DETERMINED BY X-RAYS AND OF THE TENDER AREAS ON THE SURFACE OF THE ABDOMEN.

No.	Name	Distance of the base of cap to right of mid-line in cm.		Vertical distance of base of cap above umbilicus in cm.		Shift upwards in cm.	Tender areas on the surface of the abdomen in the erect and supine positions
		Erect	Supine	Erect	Supine		
26	H. B.	4.5	7.2	1.25	8.5	2.5	Central line—whole
27	C. D.	3	4.5	4	8	4	„ upper
28	M. A. W.	2	1	8	4	4	„ middle
29	H. C. P.	5	7	(below)	(below)	1	„ „
30	S. P.	6	6	6	11	5	„ upper and middle
31	A. W.	4	7	4	0	4	„ middle
32	J. F.	3.5	4.5	(below)	9	5	„ upper
33	T. H. S.	4.5	5	1	6	5	Central line—upper and middle and right and left costal margin 7 to 9 c.c.
34	H. N.	3.5	4.5	6	11	5	Central line—upper and right costal margin 9 c.c.
35	A. K.	3.75	5	8	7	10	Central line—middle and right and left costal margins 9 c.c.
36	E. O.	4.5	6	3	9	6	Central line—upper and 4 cm. to left of lower portion of mid-line
37	A. H.	2	3	0	6	6	Right costal margin 9 c.c.
38	H. M.	4	6	0	1	1	„ „ „

two in the upper and middle portions; and in one the whole central line was tender, the maximum point being in the upper part. The area at the 9th right costal cartilage was tender in three (33, 34 and 35) of the eleven cases, and it alone was involved in two cases (37 and 38). The corresponding 9th left costal cartilage area was tender twice in two cases in which the right was also affected. The area to the left of the lower portion of the mid-line was affected once. The tenderness was present in exactly the same positions whether the patient was standing or lying. The areas of tenderness in the duodenal ulcers thus

occupied the same positions as in the gastric ulcers, namely in the middle line, at the costal margins particularly in the region of the 9th costal cartilage, and to the left of the lower portion of the mid-line.

Position of the Ulcer. Patient Standing.

Horizontal position.—The ulcer in every case was situated to the right of the mid-line, the limits being 2 cm. to 6 cm., and the average 3·9 cm.

Vertical position.—The ulcer was level with the umbilicus in two cases; 3, 4, and 8 cm. respectively below the umbilicus in three cases; and in the remaining eight from 1 cm. to 6 cm. above the umbilicus, the average being 3·7 cm.

Patient Supine.

Horizontal position.—In every case the ulcer was situated to the right of the umbilicus, the limits being 1 cm. and 7·2 cm., and the average 5·1 cm.

Vertical position.—In every case when the patient lay down the ulcer occupied a higher position than when he was standing. One was situated level with the umbilicus, one 4 cm. below, and the remaining eleven from 1 cm. to 11 cm. above the umbilicus, with an average of 7 cm. In all the cases, therefore, the ulcer shifted upwards when the patient lay down. The degree of upward shift varied from 1 cm. to 10 cm. with an average of 4·5 cm. In eleven cases the shift was upwards and outwards; in one upwards and inwards; and in one directly upwards.

In these thirteen cases the tender points obtained by light palpation of the abdominal wall were situated at quite different levels from those occupied by the ulcers both in the erect and supine positions. These tender points remained stationary whatever the position of the patient, whereas the ulcer moved upwards in the recumbent position. In those cases in which a tender area at the 9th right costal cartilage is present, the shift of the ulcer upwards and outwards in the supine position carries it in this direction, and so the two kinds of tenderness (clinical and X-ray) may be confused, but careful measurements and the dropping of the ulcer in the erect position, in most cases, are enough to prove that the fixed tender point at the 9th right costal cartilage is in the abdominal wall (figs. 8 and 9).

In view of the statement which has been made [5] that both gastric and duodenal ulcers commonly lie under the mid-line, where the point of maximum tenderness is most often found, R. Trotter has made for

me the following measurements on a separate series of cases, which prove that this statement is incorrect. The exact positions of the ulcer in fifty-two gastric and fifty-one duodenal cases were measured, in relation to the central line of the spine, in radiograms taken in the erect and supine positions at once after a barium meal. The points from which the measurements were taken were the centre of the gastric ulcer, and the centre of the base of the duodenal cap. Only one of the fifty-two gastric ulcers was situated in the mid-line and one within 1 cm. of it in

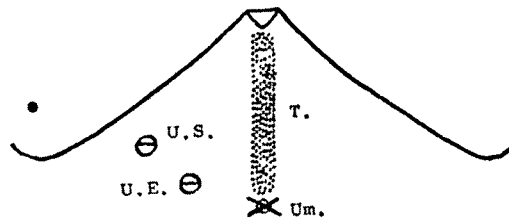


FIG. 8.—Case 26.

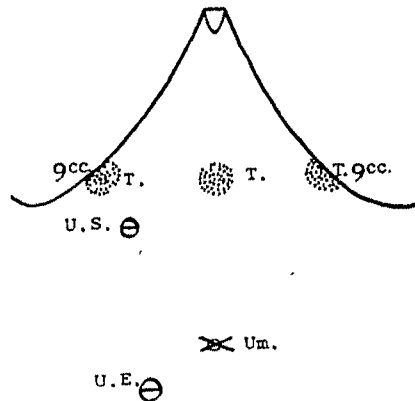


FIG. 9.—Case 35.

the erect position. The remaining fifty were situated to the left of the mid-line, at an average distance of 4.9 cm. In the supine position the ulcers shifted upwards; only one was situated centrally and the remaining fifty-one lay at an average distance of 5 cm. to the left of the mid-line. Of the fifty-one duodenal ulcers six were situated in the mid-line and three within 1 cm. of it in the erect position. The remaining forty-two were situated to the right of the mid-line at an average distance of 2.5 cm. In the supine position the ulcers shifted upwards and usually outwards; one was in the mid-line and four within 1 cm. of it; the remaining forty-six were situated at an average distance of

4.3 cm. to the right of the mid-line. The width of the epigastrium at the level of the transpyloric line varies according to the build of the patient. The average distance from the central line to the costal margin at this point is about 7 cm. Gastric ulcers are, therefore, commonly situated quite as near the costal margin as the central line at this level in both erect and supine positions. The same is true of duodenal ulcers in the supine, but not in the erect position. It may be therefore definitely stated that only a small proportion of either gastric or duodenal ulcers are situated in the mid-line in any position which the patient assumes.

FUNCTIONAL DISTURBANCES OF THE STOMACH.

Thirteen Cases (Table IV).

Certain types of functional disturbance of the stomach give rise to pain indistinguishable in all particulars from that of an ulcer. I have given reasons [6] for assuming that in the absence of complications an ulcer causes pain by acting as a focus of irritation to the neuro-muscular mechanism of the part of the stomach in which it is situated, and its symptoms are due to alterations of muscular tension; these are therefore of precisely the same nature as the symptoms of functional disorder which arise in a similar way. Many cases of functional disorder are operated on in mistake for ulcer; they can be distinguished only by the X-rays, which proves that the stomach is free from organic disease. In this group are thirteen cases and the radiographer reported that there was no ulcer nor tenderness in any part of the stomach or duodenum. All these cases showed tender areas in the anterior abdominal wall in exactly similar positions to, and indistinguishable from, those which I have described in the cases of ulcer.

TABLE IV.—TENDER AREAS ON THE SURFACE OF THE ABDOMEN IN THIRTEEN CASES OF PAINFUL FUNCTIONAL DISORDER OF THE STOMACH.

No.	Name	The areas occupied the same position in both erect and supine positions.
39	W. S.	Central line—middle
40	E. D.	„ upper
41	L. O.	„ lower
42	A. P.	„ middle
43	B. F.	„ upper
44	S. W. R.	„ upper
45	E. I.	„ upper and right costal margin 7 to 9 c.c.
46	R. S.	„ middle and right costal margin 9 c.c.
47	M. G. H.	„
48	O. P.	„ upper and 5 cm. to left of lower portion of central line
49	C. M.	Right and left costal margins 9 c.c.
50	M. P.	Right costal margin 9 c.c.
51	D. W.	5 cm. to right and left of lower portion of central line

DISCUSSION.

It is clear from a consideration of these observations that the tender areas present in the abdominal wall in cases of functional disorder of the stomach are of precisely the same nature and origin as those which occur in cases of gastric and duodenal ulcer. They are situated in similar well-defined areas, which are constant in occurrence, are fixed and immobile, and they are associated with the same type of pain although the actual source of the gastric irritation is different. They thus refer to the segment of the stomach affected irrespective of the nature of the irritant upsetting its mechanism. They are independent of any change of position of the patient and thus have no relation whatever to the position of the stomach. They have, therefore, the characters of referred pain and tenderness due to abnormal impulses originating in the viscus, which are conveyed to the spinal cord by its afferent sympathetic nerves, and their positions are determined by the distribution of those muscular and cutaneous nerves in the body wall which enter the same segments of the cord as receive the afferent sympathetic fibres from the stomach.

The following considerations prove that the distribution of the somatic nerves in the wall of the body determine the fixed positions of the pain and tenderness. In the analysis of gastric pain to which I have already referred, I found that a band of pain and tenderness involving the whole of a segmental area of the body wall was uncommon; but that it was usual for the pain to be confined to certain areas, sometimes small in extent, sometimes more diffuse; and it was not uncommon for these areas to be combined, the most frequent combination being an area at the front and another at the back. Although pain is common in the back, tenderness is a great deal commoner in front. The areas of pain are situated in the region of four vertical lines: (1) The mid-line in front; (2) a line through the nipple and costal margin, sometimes in the region of the 9th costal cartilage or sometimes higher up; (3) in the line of the angle and vertebral border of the scapula; (4) the mid-line behind, especially between the scapulæ. In these lines are distributed the terminals of the thoracic nerves, which supply both skin and underlying muscles.

After issuing from the inter-vertebral foramen each thoracic nerve divides into a posterior or an anterior division. The *posterior divisions* divide into internal and external branches which supply the muscles and integument behind the spine. The skin is chiefly supplied by the internal branches above, and by the external branches below the angle of the scapula. The internal branches issue near the spinous processes

and the external branches in the line of the angles of the ribs; the latter also travel downwards for a considerable distance before becoming superficial, and so supply the skin at a lower level than might be expected. The *anterior divisions* of the thoracic nerves pass forwards in the intercostal spaces; the upper ones, from the second to the sixth, become superficial near the sternum, and supply the skin of the mammae and the front of the thorax; the lower ones pierce the sheath of the rectus, which they supply, and become superficial near the linea alba, but some reach the skin at the outer border of the rectus and supply that on the front of the abdomen. These are known as anterior cutaneous nerves. Each of the intercostal nerves gives off a *lateral*

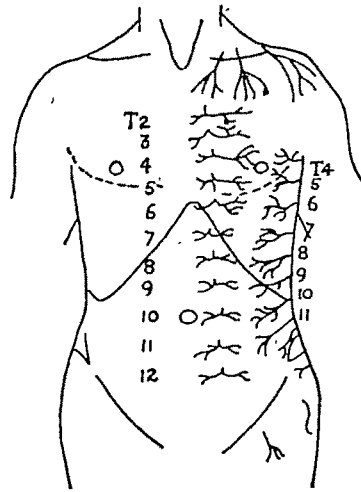


FIG. 10.—To show the terminations of the nerves in the mid-line and nipple line.

cutaneous branch midway between the vertebral column and the sternum, which pierces the muscles in a line a little behind the pectoral border of the axilla: here each divides into an anterior and posterior branch. The *upper anterior branches* pass forwards over the pectoralis major and supply twigs to the skin and the mammae; the lower anterior branches extend nearly as far forwards as the rectus, and supply the skin in a line with the upper anterior branches. The *posterior branches* pass backwards to the skin over the scapula and latissimus dorsi. A glance at the accompanying diagram (fig. 10) shows that the nerves terminate in the four vertical lines in which pain most commonly occurs.

It is a well-known axiom of medicine that in disease affecting the nerve trunks, at or near their origins, the pain is referred to the

peripheral terminations of the nerves. This distribution of the thoracic nerves is, therefore, quite a satisfactory explanation of the occurrence of the pain in these four lines. But this explanation only holds good if the irritation giving rise to the pain is situated in the spinal cord, or the origin of the nerve trunks at the terminals of which the pain and tenderness are felt. We must certainly assume this to be the case, because the pain and tenderness are segmental in distribution. The fact that pain and tenderness occur in the region of these nerve terminals, therefore, strongly supports the hypothesis that the point of irritation is in the spinal cord. This irritable focus in the spinal cord is clearly due to afferent impulses received through sympathetic nerves from the stomach.

The certainty that in conditions of gastric irritation true visceral referred pain appears does not exclude the probable occurrence of splanchnic pain of a different type as defined by Head [9]. It is not my purpose to say more about this subject, but clearly the tenderness obtained by the radiologist by heavy palpation of the ulcer demands investigation.

SUMMARY.

The observations recorded in this communication strongly support the theory of visceral referred pain as regards the abdominal viscera. The position of referred pain and tenderness due to irritation of the stomach is determined by the distribution of the intercostal nerves; it is the result of disturbance in a certain segment or segments of the stomach; and occurs, therefore, in constant and corresponding positions, whatever is the source of this disturbance.

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TUBEROUS SCLEROSIS WITH EPILEPSY (EPILOIA) IN IDENTICAL TWINS.¹

BY HOWARD FABING, M.D.

THE similarity of morbid conditions in true twins has always been a source of interest. Neuro-psychiatric disorders hold a peculiar fascination when one of the most crucial of natural experiments is conducted—the making of two persons out of one biological individual. As far back as 1883, Savage [1] reported female twins, aged 28, suffering from similar attacks of melancholia, though they lived apart. Gill [2], writing in the same year, described recurrent maniacal episodes of similar character in 20-year-old female twins.

Epilepsy in twins.—Toledo [3] studied feeble-minded girls, obviously monozygotic twins, who began having seizures at the age of eight years, within a few weeks of each other. He noted further that they had post-epileptic deliria at the same time, even if kept apart. Herrmann [4] reported monozygotic male twins, one of whom began having attacks at 13 years, and the other at 14 years. The pattern of the fits was similar in both. They began with winking, conjugate deviation of the eyes to the left, then upward deviation of the eyes, slow turning of the torso to the left, followed by fall and clonic movement in the major attacks.

Siemens [5] reported dizygotic 8-year-old males. One was very nervous and was described as neurasthenic. The other was quiet. From the age of 5 years onward the former had nervous attacks with tongue-biting. The author regards the case as probable epilepsy. Lange [6] reported five pairs of monozygotic twins, in three of which both had epilepsy, and in two of which one had epilepsy. He added three cases of undetermined zygosity, in two of which both had epilepsy, and in one of which only one had epilepsy.

Whitney [7], in a review of four cases of microcephaly in twins, states that one pair, whose cranial measurements were the same, were idio-imbeciles with epilepsy. One member of another pair in his series also had epilepsy and died in status epilepticus.

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Wilson and Wolfsohn [8] reported homologous female twins. One had "shivering" fits from the age of 3 months to 9 years; after that she had generalized grand mal attacks, and petit mal attacks as well. The other began to have fits at 13½ years, all of which were grand mal in type. They had a similar type of aura: giddiness and queer feelings. Of special interest to our study is the observation that each girl had a pigmented nævus over the right clavicle.

Luxemberger [9] found one case of dizygotic twins in which one had epilepsy. Including Lange's cases, cited above, he collected the following from the literature:—

			Both with seizures	One with seizures
Monozygotic	..	..	6	4
Dizygotic	..	..	0	7
Undetermined zygotism	..	..	3	3

He does not give specific references to his cases.

Olkon [10] observed monozygotic male twins who developed seizures at 20 months, following constipation. A study of their capillary circulation disclosed anomalies which led him to believe that their epilepsy was angiospastic in origin. Under antispasmodic therapy they remained free of seizures for three years.

Légras [11], in a study of psychoses and criminality in twins, reported that he observed two pairs of monozygotic twins, both of whom had seizures; one pair of monozygotic twins in which only one had seizures, and one pair of dizygotic twins in which but one twin was affected with epilepsy. He adds another pair of monozygotic twins, both of whom have epilepsy, seen by H. Lottig, at Nonne's clinic in Hamburg. Talbot [12], in twenty-four observations on the basal metabolic rates of eighteen pairs of twins, mentions one case of epilepsy appearing in ten-and-one-half-year old girls at the same age. Both responded favourably to ketogenic diet.

Sanders [13] reported four pairs of epileptic twins, three of which were monozygotic and one dizygotic. Eighteen-year-old monozygotic females began to have fits within one month when they were 4 years old, followed by a period of remission. One had her first grand mal attack at the age of 14, the other at the age of 15½, after being frightened at a fire. They show no mental deterioration. The father had seizures in his youth, and a maternal aunt has questionable petit mal. Both twins have a large spotted nævus (Unna).

Fourteen-year-old monzygyotic boys began to have seizures at the age of 3, six months apart. The aura in one is the sensation of a globus

followed by a disturbance of consciousness with whistling. In the other, the attacks begin with nausea and he has hallucinations of wheels turning in the right visual field. The attacks which follow are typically grand mal. Both have headache for a long period following the seizure. Both have petit mal attacks in which they talk incoherently. A sibling, as well as the father, have epilepsy.

Twelve-year-old monozygotic females both had their first seizures on the same day when they were $1\frac{1}{2}$ years old. One has had typical attacks since the age of 8 years. She is left-handed and is becoming demented. Her mental age is now 6 years 10 months. The other girl is right-handed and presents no gross mental deterioration. She has had frequent dizzy spells since the age of 4 years. No psychoses nor epilepsy are found in the family. There is twinning in the maternal family. Interscapular telangiectases are present in both.

The fourth pair in Sanders' series were dizygotic and of opposite sex, aged 5. Both began to have fits at the age of nine months, one day apart.

McBroom and Gray [14] reported $8\frac{1}{2}$ year-old monozygotic twin girls who developed seizures at the age of 5 years, one week apart. Originally, the seizure in both girls consisted of only an upward tilt of the eyes and momentary loss of consciousness. One twin has since developed more elaborate seizures, with falling, clonic movements and relaxation of the bladder sphincter. They have no aura, nor any psychic equivalents.

Rosanoff, Handy and Rosanoff [15] surveyed the problem throughout American institutions and found the surprisingly large number of twins with epilepsy as shown in the following table:—

			One with seizures	Both with seizures	Total
Monozygotic males	..	..	4	5	9
Monozygotic females	..	..	5	9	14
Dizygotic males	..	..	12	3	15
Dizygotic females	..	..	20	4	24
Dizygotic, opposite sex	..	..	32	18	45
			73	34	107

TUBEROUS SCLEROSIS.

Tuberose (or tuberos) sclerosis is the name applied by Bourneville [16] in 1880 to a rare form of multiple cerebral sclerosis occurring in young patients who had shown mental deficiency and epilepsy during life. He gave the condition its name from the potato-like appearance

and consistency of the diffusely scattered sclerotic patches. Bourneville also noted the co-existence of primitive tumours of the kidney and of skin lesions described by Balzer and Ménétrier [17] and later by Pringle [18] as adenoma sebaceum, but regarded these as coincidental. In 1895, Cesaris-Demel [19] noted the concurrence of multiple rhabdomyomata of the heart in association with tuberous sclerosis. The condition remained a pathological curiosity, though more detailed histological studies of the brain were made by subsequent workers. Gradually, the clinical syndrome of epilepsy, feeble-mindedness and adenoma sebaceum, associated with tuberous sclerosis, emerged, and in 1911 Sherlock [20] reported nine cases and gave the name "epiloia" to the symptom-complex. His choice in terminology is unusual, and I quote his reasons verbatim:—

"The term 'epiloia,' coined for the purpose, and having, the writer believes, no existing connotation, is therefore suggested. . . . It has, at any rate, some of the features which, according to Dr. Pye-Smith, characterize a good name: it is short, unmeaning, distinctive, and capable of forming an adjective" (p. 242).

Further studies have been made by Lind [21], Brushfield and Wyatt [22], who reported sixteen cases, Block [23], and others. Recently, Critchley and Earl [24] reported twenty-nine cases, and made a critical review of the literature.

Yakovlev and Guthrie [25], in a paper in 1931, enlarged the concept of this disorder to include congenital ectodermoses other than adenoma sebaceum, viz., Recklinghausen's neuro-fibromatosis and angiomas of the brain associated with naevi of the skin in the trigeminal area. They argue that these conditions merge into one another and cannot be sharply demarcated. They found fifty-five of 500 male patients in the Monson State Hospital for Epileptics afflicted with one or more of these three conditions, and state that the condition is probably far commoner than is generally supposed.

Van der Hoeve [26], in 1923, found retinal tumours in both Von Recklinghausen's and Bourneville's disease, and called them phakomata.

Farber [27] has collected forty-two cases of cardiac rhabdomyoma from the literature. Twenty-six showed associated tuberous sclerosis, five did not. In the remaining eleven the brain was not studied. To this total may be added one of Yakovlev and Guthrie's cases of tuberous sclerosis which contained a soft mass in the outer wall of the right ventricle at autopsy. Renal tumours are stated to occur in 80 per cent. of cases of tuberous sclerosis, according to Hyman [28].

This condition, in which we may find sclerotic plaques in the cortex, gliomatous tumours of the choroid plexus and ventricular wall, rhabdomyomata of the heart, primitive tumours of the kidney, tumours of the retina, abnormalities in the skin, its appendages, its blood-vessels and its pigment, associated with epilepsy and feeble-mindedness, has not been reported in twins.

A striking case of epilepsy in twins, studied on the Neurological Service of the Boston City Hospital, appears to fall into this classification.

CASE REPORT.

The patients, Dorothy and Virginia F., have just celebrated their 15th birthday. No cases of twinning are definitely known in the maternal or paternal families, but there is a vague report of twins on the paternal side which cannot be substantiated. The only known epileptic in the family is a maternal aunt, whose seizures began at the age of 30. There are two older sisters, aged 25 and 23. An older brother is aged 18, a younger sister is aged 11. No siblings have died. The girls then are fourth and fifth of six children.

Their period of gestation was normal and they were born easily. Dorothy weighed $5\frac{1}{2}$ lb. and is five minutes older than Virginia, who weighed 5 lb. They sat up, walked and talked at the normal age. When they were 15 months old Virginia had a severe lobar pneumonia, while Dorothy had a mild bronchopneumonia at the same time. At 4 years they had pertussis, at 5 years they had chicken-pox, and at 6 years they had measles.

Dorothy began to have attacks at the age of 8 years. For a year and a half they were atypical "equivalents"; she would assume a vacant expression, run headlong, grasp something and shake it. On one occasion she shook down a shelf in the bathroom after a running attack and her mother recalls another time when she ran down into the cellar and shook preserves off the shelves in the fruit closet. It was not unusual for her to run to a chair and shake it. The whole episode usually lasted about three minutes. At the age of $9\frac{1}{2}$, these running equivalents were replaced by true convulsive seizures. They now occur about every two to three weeks and are often serial; three seizures in one day is a common occurrence. The aura is a "funny thought." On questioning her closely Dorothy says that her trend of thought suddenly changes and she seems to get a mental glimpse into future events. No hallucinations are associated. She describes this prescience to her mother who chides her for "borrowing trouble." Sometimes she gets the "funny thought" but is able to "fight off" the fit. These are obviously petit mal attacks. The aura is quickly followed by loss of consciousness which lasts five minutes. During the seizure there are typical clonic and tonic movements. She is seldom incontinent of urine and faeces during the attack but often hurts herself in falling. A period of confusion of about three minutes follows the attack.

Virginia's seizures began about a year and a half ago, at the age of 13½ years. They are always nocturnal, occurring usually in the hours after midnight, about once a week. She had an aura of "melancholy," as her mother calls it, for about a half-day before the attack. Her parents, by noticing her glumness and retarded activity, can prognosticate the advent of an attack. Further investigation of the "melancholy" reveals that thoughts of death, God, Christ, and heaven, flit through the girl's mind in a jumbled way, three

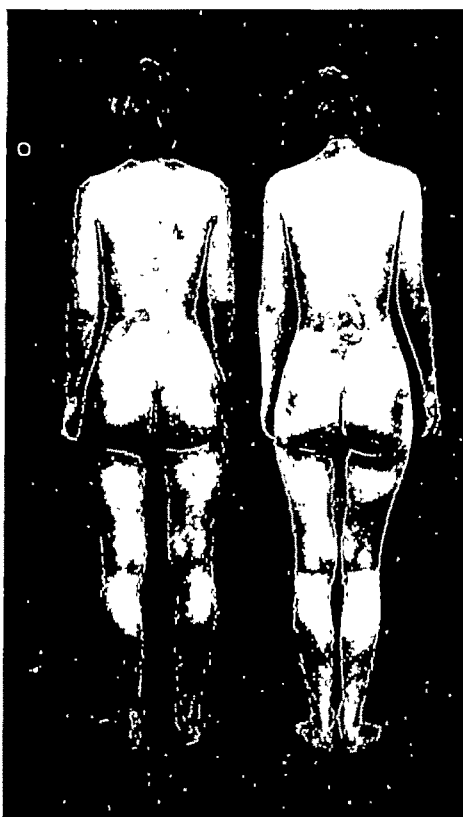


FIG. 1.—Note mirror-image distribution of nevi at the level of L2 spine.

or four times on the afternoon preceding a seizure. Visual, auditory, or gustatory hallucinations are not associated; the episodes are composed solely of abstract thought. They upset her so completely that she often stands with arms outstretched, "like Jesus on the cross," at such times. One afternoon, while they were in the hospital, Dorothy remarked, "Virginia's melancholy to-day. She's thinking about religion again. She's going to have a spell to-night." The seizure occurred.

As Virginia's major attacks occur during sleep, no aura precedes them

immediately. They are evidenced by tonic and clonic convulsions, and she is often incontinent of urine and faeces. Following the seizure, she sleeps until her usual waking time, and has no knowledge that a fit has occurred. She is not drowsy the following day.

The girls are in the first year of high school. They were promoted each year except their first year in grammar school, when illness (measles) kept them from attending school regularly. Virginia does better in school, on the whole, in spite of the fact that Dorothy is much more a "plugger." Virginia's disposition is better; she is less prone to bicker and argue than Dorothy. Virginia is a night prowler; Dorothy sleeps well. Virginia has always been thinner than Dorothy. At the present time their weights are 105 lb. and 115 lb. respectively. Their friends and associates are different, chiefly because the children of the neighbourhood keep away from Dorothy because she has



Dorothy.

Virginia.

FIG. 2.—Right facial weakness.

Left facial weakness.

fits. Virginia, whose seizures are confined to her bedroom, escapes such social segregation.

The girls are 5 ft. 4 in. tall, and are pubescent. Dorothy is the heavier, and is inclined to be somewhat pot-bellied. The integument is of chief interest. They each have a diffuse acneiform eruption on the face which assumes a butterfly distribution. On close inspection, in addition to comedones of *acne vulgaris*, many small hard red papules are found. These have been present for the past two or three years and defy treatment. Dorothy has a vascular naevus of the capillary type on the right neck anteriorly. Virginia has two naevi of the same type on her left anterior neck. Dorothy has a series of small pigmented raised naevi on her left back at the level of vertebra L2. Lateral to this is a large naevus anemicus (of Vornor). Virginia has a series of fibromata mollusca at the same level on the right side. Above these is a naevus anemicus of Vornor. In addition, there is a small cluster of naevi of the fibroma molluscum type at the mid-dorsal level on the left.

The only other physical findings of note is a slow irregularity of Virginia's heart. Clinically, this was thought to be auricular fibrillation, but electrocardiogram shows frequent premature auricular beats with aberrant ventricular responses.

The neurological examination discloses facial weakness to emotional stimulation in both girls, Dorothy's on the right, and Virginia's on the left. The remainder of the neurological examination was negative.

LABORATORY DATA.

	<i>Dorothy</i>				<i>Virginia.</i>
Urinalysis	Normal	..	..	..	Normal
Blood picture ..	Normal	..	..	..	Normal
Lumbar puncture—					
Initial pressure	120	..	..	..	165
Colour	Clear, colourless	..	..	..	Clear, colourless
Dynamics ..	Normal	..	..	..	Normal
Cells	0	..	..	..	1 lymphocyte
Protein	20 mgm. per cent.	..	..	..	20 mgm. per cent.
Gold sol	0000000000	..	..	..	0000110000
Wassermann—					
Spinal fluid ..	Negative	..	..	..	Negative
Blood	Negative	..	..	..	Negative
Basal metabolism ..	± 0	..	..	..	-10.5 per cent.
Glucose tolerance test ..	Slight delay in return to normal level				Normal
Intelligence quotient ..	64	..	..	..	76
X-rays of skull ..	Negative	..	..	..	Negative
Encephalogram ..	Within normal limits	..	..	..	The same
Teleorontgenogram of heart	Normal size and configuration	..	..	..	The same
Fluoroscopic study of heart	No abnormalities	..	..	..	The same
Fluoroscopic study of abdomen	No situs inversus viscerum	..	..	..	The same
Uroselectan study of kidneys	Normal	..	..	..	Bifurcation of right ureter with double pelvis of the right kidney

The immediate family of the twins was inspected for the presence of nævi. The father, the oldest sister (aged 25), the brother (aged 18), the younger sister (aged 11), are all singularly free of any nævi. The mother has a small fibroma molluscum in the left nasolabial fold and two other soft fibromatous tumours in the forehead. The second oldest daughter (aged 23) has a conspicuous melanoma in the intergluteal fold, but is otherwise free of nævi.

COMMENT.

The diagnosis of tuberous sclerosis in these girls is made on the basis of their varied skin lesions, their epileptiform seizures, and their mental

impairment. They have been followed for nine months, and the condition is progressing. They now show more marked facial lesions which look less like acne vulgaris and more like true adenoma sebaceum. That a definite element of deterioration is present in the mental sphere is attested by the fact that Virginia (who was described as the more docile of the two, and whose intelligence quotient was the higher) became such a serious behaviour problem recently that care in an institution became necessary. She split her mother's scalp with a coat-hanger, refused to leave a neighbour's house, threw a stone through a window, and ran away repeatedly. The parents are reconciled to placing the other girl, Dorothy, in an institution also, because she becomes progressively more "bull-headed." Under rather large doses of luminal, seizures have decreased in frequency in both girls.

The cardiac irregularity in Virginia, with the electrocardiographic evidence of frequent extrasystoles arising in the auricles, with aberrant ventricular response, points to a lesion in the conduction mechanism. In the absence of any rheumatic history, and in the presence of tuberous sclerosis, a diagnosis of cardiac rhabdomyoma is not a remote assumption. No cardiac tumour is demonstrable with the aid of the X-ray, however, and the suggestion is advanced modestly, since a study of the literature fails to disclose any previous instance of an ante-mortem diagnosis of cardiac rhabdomyoma. The anomalies discovered in Virginia's right kidney are not inconsistent with a primitive kidney tumour in association with tuberous sclerosis.

The striking mirror-imaging of the skin lesions raises interesting speculations concerning development. The same reasoning may be applied here as in the case of situs inversus viscerum and other mirror-image displacements in identical twins: that the accessory cleavage which divided the zygote into two occurred after polarization of the zygote into right and left halves. If this be granted, the assumption is clear that the lesion which was destined to evidence itself as tuberous sclerosis was present in the very early life of the zygote—shortly after the insemination of the ovum. The temptation arises to assume that the "pre-tuberous sclerosis" lesion was present in the zygote at its beginning, i.e., that the lesion is truly hereditary, or genotypical. However, this is not a necessary deduction, and it may be argued with equal justice that a blastophoric influence—or injury to the zygote—occurred early in its life, and left its mark in the form of tuberous sclerosis.

If a series of dizygotic twins having this symptom-complex could be

studied, the answer to the question of true heredity versus blastophoria could probably be given. If both twins exhibited the disease in nearly equal intensity in all cases, a blastophoric influence, or an intra-uterine environmental influence, would be indicated. If, on the other hand, only one of dizygotic twins exhibited the disease in a series of cases the assumption of genotypical, or truly hereditary, influence would be correct, since dizygotic twins are but siblings, and have differing genoplasm.

In this connection, the only study of *nævi* in twins is that of Siemens [5] in 1924. He made actual numerical counts of various types of *nævi* in monozygotic twins, dizygotic twins, and in non-siblings of the same age. He found that the correlation of *nævus* counts was twice as close in one-egg twins as in two-egg twins, and that the correlation was twice as close in the latter as in non-siblings of the same age. He states, "These findings give us the exact numerical proof that the number of *nævi* which an individual possesses is definitely dependent on his hereditary *anlagen*" (p. 24). This, perhaps, is an over-statement.

There is also evidence of mirror-image lesions in the central nervous system in these twins. This is plain when it is recalled that one twin exhibits a right facial weakness while the other shows the same weakness on the left. Furthermore, it is worth noting that the aura of the fit in each girl is a voluminous mental state, indicating that the seizure has its inception in the temporo-sphenoidal lobe in both cases. Whether one girl has a right temporal and the other a left temporal lesion is not demonstrable. To find a parallelism between skin and central nervous system lesions in this condition is to be expected, however, when their common ectodermal origin and common metameric segmentation is remembered. In 1915, Cobb [29] reported a case of hemangioma of the spinal cord at the level of the tenth dorsal segment associated with a series of skin *nævi* of the same metamere. Other similar instances are quoted by Yakovlev and Guthrie [25].

SUMMARY.

- (1) The literature on epilepsy in twins is reviewed.
- (2) The syndrome of tuberous sclerosis with epilepsy (*epiloia*) and allied condition is outlined.
- (3) A case of epilepsy in monozygotic twins resulting from tuberous sclerosis is reported.
- (4) A diagnosis of probable rhabdomyoma of the heart and primitive kidney tumour in one of the twins is advanced.

(5) The mirror-image position of the skin and central nervous system lesions, similar to situs inversus viscerum and other transpositions frequently found in monozygotic twins, is noted, and from this observation the deduction is made that the anlagen of the lesions of tuberous sclerosis and allied conditions are present in the very early life of the zygote.

(6) The question of genotypical heredity versus blastophoric injury in the production of tuberous sclerosis, as raised by these cases, is discussed.

I wish to thank Dr. William G. Lennox and Dr. Stanley Cobb for the privilege of publishing these observations on their cases, and Dr. P. I. Yakovlev for his interest and assistance.

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A STUDY OF THE MUSCLE CHEMISTRY IN MYASTHENIA GRAVIS, PSEUDOHYPERTROPHIC MUSCULAR DYSTROPHY AND MYOTONIA.¹

By S. NEVIN.

IN recent years, the advances which have been made in the study of the chemistry of skeletal muscle have revealed that certain organically bound phosphorus compounds, namely creatine phosphoric acid (phosphagen), adenosine triphosphoric acid (adenyl pyrophosphate), and certain soluble carbohydrate esters, play a very important rôle in the chemical processes subserving muscular contraction. The details of these chemical processes are not yet fully understood; but the changes in the concentration of the phosphorus holding compounds following contraction are well recognized. These changes have been examined in muscle obtained at biopsy from cases of myasthenia gravis, pseudohypertrophic muscular dystrophy and myotonia, with a view to determining the presence or otherwise of any abnormality in the intrinsic chemical mechanism of the muscle in these diseases. Much work of a biochemical nature has been done in the study of these diseases, but this has been confined almost entirely to the examination of substances in the blood and urine related to the metabolism of muscle. The results of these studies have been inconclusive, and they will not be reviewed in detail, but only referred to later in so far as they may be related to the results of the present study.

BASIS OF THE INVESTIGATIONS AND METHODS OF ANALYSIS.

It is essential briefly to outline the chemical changes accompanying muscular contraction, so far as they are at present known, in order that the changes in the phosphorus holding compounds, and their importance, may be better understood.

There are two main chemical processes accompanying muscular contraction, namely, the breakdown of creatine phosphoric acid and the production of lactic acid. In resting muscle creatine phosphoric acid and adenosine triphosphoric acid are present in high concentration, each amounting approximately to 40 per cent. of the total acid-soluble phosphorus. On the other hand, the soluble carbohydrate esters

¹ This work was done during the tenure of a Halley Stewart Research Scholarship at the Neurological Research Unit, National Hospital, Queen Square, London.

(including under this heading glycerophosphoric acid, &c.) are present in small amount. On contraction the earliest chemical change is the anaerobic breakdown of creatine phosphoric acid into its constituents, creatine and phosphoric acid. Adenosine triphosphoric acid also probably breaks down early during contraction into inosinic acid, ammonia and phosphoric acid. Glycogen by enzymic hydrolysis gives rise to hexose. This unites with the phosphoric acid molecules set free in the other reactions to form hexose monophosphate, from which by a series of changes lactic acid is produced. There is thus produced in the contracted muscle a diminution of the creatine phosphoric acid and adenosine triphosphoric acid, with an increase in the soluble carbohydrate esters and in the free orthophosphate. This altered distribution in rabbits' muscle is shown in Table I, from Milroy [1]. These changes

TABLE I.

	Biceps femoris (resting)		Same (after seven minutes' tetanus)	
	Mg	Per cent. of total	Mg.	Per cent. of total
Total acid-soluble, P. per g. muscle	1.387	—	1.387	—
Of this:				
As free orthophosphate	0.265	19.1	0.798	57.5
Phosphagen	0.882	27.5	0.057	4.1
Mono-ester	0.198	14.2	0.234	16.8
Adenyl pyrophosphate	0.456	32.8	0.310	22.8
Recovered	1.801	93.6	1.399	100.7

are reversible. Recovery takes place partly anaerobically and is completed aerobically when the creatine phosphoric acid and adenosine triphosphoric acid are resynthesized, while the lactic acid is in part oxidized but largely reconverted into glycogen. The relation of these chemical processes to one another and to the development of tension in the muscle is very obscure and will not be discussed. The importance, however, of the changes in the phosphorus-holding compounds during muscular contraction, especially the breakdown of creatine phosphoric acid, is apparent, and a study of these changes may be presumed to give some definite indication as to the presence or otherwise of any abnormality in the intrinsic chemical mechanism in pathological muscle.

To study pathological muscle the plan of investigation was as follows:—

The affected muscle was exposed at biopsy under local anaesthesia in different cases. A sample of resting muscle weighing approximately 0.5 to 1 g.

was quickly removed and placed in liquid air. The exposed muscle was then thrown into contraction for three to five minutes by faradic stimulation applied locally with silver wire electrodes coated with silver chloride. A portion of this muscle was removed immediately in the contracted state, and another portion after forty-five minutes had elapsed to allow for the recovery changes to take place. These samples were also frozen in liquid air and all three were then analysed for the distribution of the phosphorus-holding compounds. The results were compared with similar experiments carried out in rabbits under amytal and ether anaesthesia, and with the analysis of resting and contracted normal human muscle obtained at operation.

The method employed in the analysis of the muscle was as follows:—

The frozen muscle having been weighed, was extracted with 10 to 15 c.c. of 5 per cent. ice-cold trichloroacetic acid after being thoroughly ground with quartz sand in an ice-cold mortar. The extract was filtered by suction into a graduated test tube placed in a freezing mixture, and was immediately rendered faintly alkaline with 40 per cent. NaOH. This extract contained free orthophosphate, creatine phosphoric acid, adenosine triphosphoric acid, and soluble carbohydrate esters. Using Fiske and Subbarow's method of phosphorus estimation, the creatine phosphoric acid and the orthophosphate were determined by precipitation of the latter by 10 per cent. calcium chloride in calcium hydroxide. The adenosine triphosphoric acid was determined by hydrolysis of the original extract for seven minutes in normal HCl at 100° C., the usual calculation then being made, and the soluble carbohydrate esters were calculated by difference from the total phosphorus in the original extract. The calcium precipitate was also examined for insoluble esters other than the readily hydrolysable adenosine triphosphoric acid and when possible the colour development method was also used in the estimation of the creatine phosphoric acid.

RESULTS OF INVESTIGATION OF NORMAL MUSCLE.

In the experiments in rabbits the extensor muscles of the leg were used. Contraction was produced for three minutes; forty-five minutes were allowed for recovery. Table II gives an example of the findings

TABLE II.

	Resting		Contracted		Recovered	
	Mg	Per cent. of total	Mg.	Per cent. of total	Mg.	Per cent. of total
Total acid-soluble P. per g. of muscle	1.766	—	1.659	—	1.641	—
Of this:						
As free orthophosphate ..	0.210	11.9	0.880	53.0	0.202	12.3
Creatine phosphoric acid ..	0.714	40.4	0.108	6.5	0.744	45.3
Adenosine triphosphoric acid	0.768	43.2	0.499	30.1	0.625	38.1
Soluble esters	0.079	4.4	0.172	10.4	0.070	4.3

TABLE III.

	1			2			3			4			5			6		
	Mg.	Per cent. of total	Mg.	Mg.	Per cent. of total	Mg.	Mg.	Per cent. of total	Mg.	Mg.	Per cent. of total	Mg.	Mg.	Per cent. of total	Mg.	Mg.	Per cent. of total	Per cent. of total
Total acid soluble P. per g. muscle	1.245	—	1.261	—	—	1.212	—	—	1.328	—	—	1.159	—	—	0.908	—	—	—
Of this: As free ortho-phosphate	0.191	15.3	0.168	13.4	0.169	13.9	0.148	11.1	0.136	11.7	0.858	89.0	0.191	11.2	0.375	89.1	—	—
Creatine phosphoric acid	0.517	41.5	0.515	40.8	0.536	44.2	0.566	42.7	0.503	43.3	0.081	8.9	0.509	43.5	0.135	14.1	—	—
Adenosine triphosphoric acid	0.519	41.7	0.564	44.7	0.474	38.1	0.588	44.3	0.514	44.3	0.294	32.5	0.504	43.1	0.253	26.3	—	—
Soluble esters	0.018	1.4	0.018	1.0	0.083	2.7	0.026	1.8	0.007	0.6	0.177	19.5	0.036	2.2	0.197	20.6	—	—

in several rabbit experiments. The recovery of the adenosine triphosphoric acid and soluble carbohydrate esters was slower than that of the creatine phosphoric acid, and was usually not complete within the time of the experiment.

Through the kindness of Mr. Julian Taylor and Mr. Harvey Jackson, normal human muscle was obtained from the pectoralis major during operations on the breast. Table III gives the results of six analyses. In two cases it was possible to stimulate the muscle for five minutes after removal of the resting sample.

Tables II and III give the normal distribution of the phosphorus-holding compounds in muscle, and the degree of change produced by a given form of stimulation and subsequent to recovery. •

RESULTS OF INVESTIGATION OF PATHOLOGICAL MUSCLE.

A brief clinical summary of the cases investigated is given at the end of the paper.

MYASTHENIA GRAVIS.

The biopsy was performed on the right rectus femoris muscle. The muscle was normal in appearance and contracted strongly on direct electrical stimulation. This was continued for five minutes, and forty-five minutes were allowed for recovery. The analyses are given in Table IV.

TABLE IV.

	Resting		Contracted		Recovered	
	Mg.	Per cent. of total	Mg.	Per cent. of total	Mg.	Per cent. of total
Total acid-soluble P. per g. of muscle	1.895	—	1.218	—	1.090	—
Of this :						
As free orthophosphate ..	0.150	10.7	0.448	36.8	0.135	12.4
Creatine phosphoric acid ..	0.566	40.6	0.163	13.4	0.445	40.8
Adenosine triphosphoric acid	0.588	38.6	0.369	30.8	0.349	32.0
Soluble esters	0.141	10.1	0.243	19.9	0.161	14.8
Insoluble esters	0	—	0	—	0	—

These analyses of the phosphorus holding compounds in this case of myasthenia gravis are of the same order as in normal muscle, and one may therefore conclude that it is improbable that in this disease there is any abnormality in the intrinsic chemical mechanism. If such were present, one would expect some abnormality in the normal phosphorus

distribution in the resting state, and of this there is no evidence, the slight increase in soluble carbohydrate esters being without significance. Further, on contraction by electrical stimulation of the muscle, the changes in the phosphorus distribution occurred to the same extent as in normal muscle and these changes were nearly completely reversed by a period of recovery. It is therefore justifiable to conclude that the chemical processes which accompany activity and recovery in the myasthenic muscle differ in no significant way from those which are characteristic of healthy muscle.

CASE OF MUSCULAR WEAKNESS ASSOCIATED WITH GRAVES' DISEASE.

The biopsy was performed on the right vastus lateralis. The muscle, which was normal in appearance, was stimulated for three minutes, and forty-five minutes were allowed for recovery.

The analyses which are given in Table V show normal chemical changes. The phosphorus distribution in the resting muscle is perfectly normal, and although the changes on contraction are not so great as were found in normal muscle, this is accounted for by the fact that the muscle was stimulated for three minutes only. The high accumulation of soluble esters might be considered abnormal, but their removal during recovery was so complete as to make this improbable.

TABLE V.

	Resting		Contracted		Recovered	
	Mg.	Per cent. of total	Mg.	Per cent. of total	Mg.	Per cent. of total
Total acid-soluble P. per g. of muscle	1.116	—	1.269	—	1.053	—
Of this :						
As free orthophosphate ..	0.104	9.3	0.149	11.7	0.129	12.2
Creatine phosphoric acid ..	0.460	41.2	0.850	27.6	0.480	40.8
Adenosine triphosphoric acid	0.508	45.5	0.465	36.6	0.442	42.0
Soluble esters	0.044	3.9	0.805	24.0	0.052	4.9
Insoluble esters	0	—	0	—	0	—

The relation of this case, on the one hand, to the muscular weakness which is a common symptom in Graves' disease, and, on the other, to the fully developed picture of myasthenia gravis which is occasionally found associated with Graves' disease, is not clear. It is improbable, however, from these biochemical studies, that abnormalities in the

muscle chemistry are the cause of the loss of muscle function in such cases.

CASE OF PERIODIC MUSCULAR WEAKNESS.

This case was examined as one of myasthenia, and the chemical findings may suitably be given here, although the histological examination of the muscles makes the true nature of the case uncertain. The outstanding clinical feature of the case was the extreme weakness of the muscles without wasting, especially in the deltoid muscles. The biopsy was performed on the left deltoid, and the plan of the experiment was altered in that after the sample of resting muscle had been removed, the patient was made to contract his muscle as strongly as possible. After a portion of this contracted muscle had been removed, electrical stimulation, which had to be weaker than usual owing to the fact that the main nerve was not blocked, was carried out for eight minutes. This electrically contracted muscle was also examined; the examination of recovered muscle was omitted. The analyses are given in Table VI:—

TABLE VI.

	Resting		Voluntarily contracted		Electrically contracted	
	Mg.	Per cent. of total	Mg.	Per cent. of total	Mg.	Per cent. of total
Total acid-soluble P. per g. of muscle	1.018	—	0.989	—	0.902	—
Of this:						
As free orthophosphate ..	0.118	11.6	0.125	12.6	0.218	24.2
Creatine phosphoric acid ..	0.459	45.1	0.427	43.2	0.238	26.4
Adenosine triphosphoric acid	0.394	38.7	0.406	41.0	0.327	36.2
Soluble esters	0.047	4.6	0.031	3.1	0.119	13.2
Insoluble esters	0	—	0	—	0	—

The resting muscle is seen to be perfectly normal as regards the phosphorus holding compounds, and voluntary contraction has produced only slight chemical changes in these compounds, or such as were reversible during the contraction. On the other hand, weak electrical stimulation has produced considerable chemical change. This shows definitely that in this muscle, which was extremely weak, an abnormal chemistry was not the cause of weakness. The case is of interest as showing the stability of the intrinsic chemical mechanism and how it may be normal in the presence of gross disturbances of muscle function.

PSEUDOHYPERTROPHIC MUSCULAR DYSTROPHY.

Case 1.—The biopsy was performed on the left soleus muscle. The muscle was paler than normal, and fibrous. Stimulation produced good contraction, and was carried out for eight minutes, when the muscle appeared to be fatiguing. Forty-five minutes were allowed for recovery. The analyses are given in Table VII.

TABLE VII.

	Resting		Contracted		Recovered	
	Mg	Per cent. of total	Mg.	Per cent. of total	Mg.	Per cent. of total
Total acid-soluble P. per g. of muscle	0.418	—	0.298	—	0.228	—
Of this:						
As free orthophosphate ..	0.067	16.0	0.059	19.9	0.047	21.1
Creatine phosphoric acid ..	0.187	82.8	0.069	23.3	0.068	80.5
Adenosine triphosphoric acid	0.178	42.6	0.097	32.4	0.085	88.1
Soluble esters	0.036	8.6	0.078	24.4	0.023	10.8
Insoluble esters	—	—	0	—	—	—

Case 2.—The biopsy was performed on the right infraspinatus muscle which clinically showed pronounced pseudohypertrophy. The muscle was extremely degenerated and infiltrated with fat, and only feeble contraction resulted from electrical stimulation. This was carried out for five minutes, and examination of the recovered muscle was omitted. The results are given in Table VIII, and included for comparison is the analysis of resting muscle from a case of muscular atrophy secondary to nerve degeneration. This muscle failed to react to electrical stimulation.

TABLE VIII.

	Myopathy resting		Myopathy contracted		Secondary atrophy	
	Mg.	Per cent. of total	Mg.	Per cent. of total	Mg.	Per cent. of total
Total acid-soluble P. per g. of muscle	0.079	—	0.089	—	0.359	—
Of this:						
As free orthophosphate ..	0.021	26.6	0.025	28.1	0.102	28.4
Creatine phosphoric acid ..	0.015	19.0	0.012	13.5	0.047	13.1
Adenosine triphosphoric acid	0.028	35.4	0.031	34.8	0.120	33.4
Soluble esters	0.015	19.0	0.021	23.6	0.090	25.1

These analyses of the phosphorus holding compounds in muscular dystrophy show a deviation from the normal in the following respects:—The total acid-soluble phosphorus is extremely low and varies widely throughout the muscle. The creatine phosphoric acid content of the resting muscle is definitely below normal and the breakdown of this substance on stimulation is also less than normal. In the first case the distribution and changes on contraction in the other compounds are not significantly altered, but in the extremely degenerated muscle of the second case, there is a considerable accumulation of soluble esters.

The low total acid-soluble phosphorus is obviously accounted for by the increase of fat and fibrous tissue in the muscle. Regarding the changes from the normal, in the creatine phosphoric acid, it is impossible to make a definite statement. These changes have not been considered indicative of a primary bio-chemical abnormality in the disease but rather secondary to the muscular degeneration for the following reasons:—

(1) If there is in muscular dystrophies a primary failure of the muscle to build up creatine phosphoric acid, it is to be expected that the diminution of this compound in the muscles would be much more considerable than has actually been found. Even in the muscle in the second case, which contains much less than one-tenth of the total acid-soluble phosphorus of normal muscle, there is still 19 per cent. of creatine phosphoric acid.

(2) In atrophied muscle secondary to nerve degeneration, a similar and even greater fall in the creatine phosphoric acid content of the muscle has been found.

(3) Lastly, as shown especially in Case 1, the usual chemical changes in the phosphorus holding compounds take place during contraction, although to a lesser degree, and the creatine phosphoric acid which is broken down is built up again during recovery to nearly its original value; therefore creatine phosphoric acid can be built up in the muscle; but why in degenerating muscles it should be much less in amount as compared with the adenosine triphosphoric acid, it is impossible at present to explain.

CASE OF DYSTROPHIA MYOTONICA.

The biopsy was performed on the right flexor carpi radialis. The experiment was performed after myographic records had been taken, and it was only possible to examine the resting muscle and contracted muscle after weak stimulation for five minutes. The analyses are given in Table IX.

TABLE IX.

	Resting		Contracted	
	Mg.	Per cent. of total	Mg.	Per cent. of total
Total acid-soluble P. per g. of muscle	0.582	—	0.691	—
Of this:				
As free orthophosphate	0.118	19.4	0.189	27.3
Creatine phosphoric acid ..	0.185	31.8	0.204	29.5
Adenosine triphosphoric acid ..	0.210	36.1	0.192	27.8
Soluble esters	0.074	12.7	0.106	15.3
Insoluble esters	—	—	0	—

These figures for the phosphorus holding compounds of muscle in myotonia also show slight differences from the normal. The total acid soluble phosphorus is below normal, and there is a slight diminution of the creatine phosphoric acid content with less change than normal in this compound on contraction. The other compounds are not significantly altered. Whether these changes from the normal indicate a primary disturbance in the intrinsic chemical mechanism of the muscle or are indicative of some other abnormality of the muscle, excitatory or otherwise, it is impossible to state.

The breakdown of creatine phosphoric acid appears such an important reaction in the chemistry of normal muscular contraction that the change in this reaction found in a disease like myotonia cannot be considered insignificant.

On the other hand the deviation from the normal is not considerable and there is no gross accumulation of one or other compound at any stage of activity. Also, somewhat similar changes have been found in the cases of muscular dystrophy. Therefore it may be that the creatine phosphoric acid mechanism is in some way easily altered by diseased conditions of muscle, although the mechanism itself may not be primarily at fault. This appears the most likely explanation. In any case it seems clear that in the further study of the aetiology of this disease the biochemical investigations must be correlated with electrical studies of the excitation of the muscle.

DISCUSSION.

The results of the above investigations of the phosphorus holding compounds in muscle from cases of muscular dystrophy, myasthenia gravis and myotonia have some relation to the recent work on the metabolism of creatine in these diseases.

In 1929, Brand *et al.* [2] found that the constant creatinuria occurring in cases of muscular dystrophy could be increased 40 per cent. by the administration of glycine and to a less extent by some other amino acids.

Milhorat, Techner and Thomas [3] [4] investigated these changes in more detail, and found that after a period of two to eight weeks the increased creatinuria ceased, and at this stage a considerable clinical improvement took place in the patients. This improvement Milhorat considered might be due to an increased creatine phosphoric acid content of the muscles.

Kostakow and Slauck [5] [6] also suggested from their work on this subject that the underlying disturbance in muscular dystrophy might be the inability to absorb and utilize creatine and that this was restored by glycine, which altered the phosphagen content of the muscles.

Tripoli and Beard [7], discussing the effect of glycine and other amino-acids in muscular dystrophy, state "the creatine retained as phospho-creatine (creatine phosphoric acid) serves over and over again to supply the energy for muscle contraction, and the muscular efficiency of the patient increases at a remarkable rate."

Two questions obviously arise in respect of this work; first, the possible explanation of muscular dystrophy as a disturbance of creatine metabolism and, second, the effect of glycine in the treatment of this disease. With regard to the first question, reasons were given earlier in this paper for regarding the alterations found in the creatine-phosphoric acid in the muscles in this disease as secondary to the muscle degeneration. One ventures to suggest that the alterations in creatine metabolism may be similarly explained. It is probable that creatine is formed in the body at a definite rate, under conditions at present unknown, from specific amino-acids of which glycine is a very important one, and is stored or metabolized almost entirely in the skeletal muscles. In the resting state of the muscle it is mostly found in combination with phosphoric acid, forming creatine phosphoric acid. In adult males all the creatine formed in the tissues is stored or metabolized in the muscle and none appears in the urine. In children some creatine is excreted in the urine and the total creatine co-efficient may be as high as in men. This is due to the production of creatine in excess of the needs of the muscular system at this stage of growth and when the muscular system reaches its average percentage of the total body-weight, the creatinuria ceases. In muscular dystrophy, owing to the excessive degeneration of

the muscle, all the creatine formed in the body cannot be stored or metabolized by the muscles, and some is excreted just as it may be after a recent loss of muscle tissue through the amputation of a limb. Glycine when given in large doses, evidently leads to an increased production of creatine for the time being, and this leads to increased excretion. This effect is not specific for cases of muscular dystrophy and will occur in excessive wasting or disuse of muscles from any cause. It has been found in a case of progressive muscular atrophy (personal examination) to a degree comparable with that which occurs in muscular dystrophy. Further, there is no evidence that in muscular dystrophy there is any such deficiency of creatine for the needs of muscles as would lead to a failure of phosphagen synthesis. In these cases the total creatine co-efficient is generally within the lower limits of normal, indicating, rather an excess of creatine which cannot be metabolized by the muscles, and the administration of glycine appears only to add to this excess.

With regard to glycine as a therapeutic agent in muscular dystrophy, some workers have failed to find any improvement (Brand [8]). In those cases in which improvement has been found it is possible that the specific dynamic effects of such large doses of the amino-acid glycine may lead to some stimulation of metabolism in the degenerating muscles, and thereby produce some subjective improvement.

Morgulis and Young [9] deduce, from their study of the creatinuria occurring in a case of myotonia atrophica, that in this disease there is an inability of the muscle to synthesize phosphagen. The explanation given above for the creatinuria occurring in muscular dystrophy also applies here, and the findings given in this paper respecting the creatine phosphoric acid content of the muscles in a case of dystrophia myotonica do not appear to support the view that in this disease there is a failure of the muscle to synthesize phosphagen.

Boothby [10] considered it possible that, as cases of myasthenia gravis excrete small quantities of creatine, the beneficial effects of glycine, presumably from building up the phospho-creatine content of the muscle, would be as likely to occur in this disease as in muscular dystrophy. He has reported considerable success in several cases of myasthenia gravis treated with glycine. In a later paper Boothby [11] reported that there may occur in myasthenia gravis after glycine an increased creatinuria which later falls, and that the clinical improvement may be coincident with this fall.

Remen [12] also found improvement in myasthenia by glycine

therapy, and concluded that in myasthenia gravis there is a disturbance of creatine creatinine metabolism which can be corrected with glycine, and that this disturbance may be a failure of the muscle to build up creatine phosphoric acid. This seems improbable from the results of the investigation of creatine phosphoric acid in myasthenic muscle recorded in this paper. Further, in the case of myasthenia gravis, in which the phosphorus holding compounds were found normal, a considerable increase in creatinuria was produced by glycine; yet apart from the administration of glycine the muscles in this case showed a normal content of creatine phosphoric acid. In this disease, as in muscular dystrophy, these alterations in creatine metabolism appear to be secondary effects of the disease. Also they are less constant in myasthenia gravis; and in a case affected equally to the above-mentioned case as regards the general musculature, no creatinuria was found after glycine. The effect of glycine as a therapeutic agent is another question. If it is beneficial, it is unlikely that it acts through the alteration which it produces in the creatine metabolism.

In myasthenia gravis it would appear therefore that future studies as regards its aetiology should be directed to the investigation of excitatory transmission at the neuro-muscular junction, rather than along metabolic lines. It is at the neuro-muscular junction that ephedrine, the administration of which is commonly followed by some improvement in myasthenia gravis, is most likely to act.

SUMMARY.

(1) The phosphorus holding compounds of muscle have been studied in cases of myasthenia gravis, pseudo hypertrophic muscular dystrophy and myotonia.

(2) In myasthenia gravis they have been found normal, and it has been concluded that this disease is not associated with an abnormality in the intrinsic chemical mechanism of muscular contraction.

(3) In pseudo hypertrophic muscular dystrophy and myotonia some alterations from the normal have been found, the significance of which has been discussed.

(4) The recent work on creatine-metabolism in cases of myasthenia gravis, pseudo hypertrophic muscular dystrophy and myotonia has been discussed in relation to the results of the present investigation.

My best thanks are due to Professor T. H. Milroy for his criticism and advice, to the Honorary Physicians at the National Hospital for permission to use their cases, and to Mr. Pennybacker for assistance with the biopsies.

CLINICAL SUMMARIES OF THE CASES INVESTIGATED.

Case of Myasthenia gravis.

M. O'B., a female, aged 32, was admitted to the National Hospital, under Dr. Carmichael, on February 30, 1932. Three years before admission she began to complain of symptoms of general weakness, which became worse over a period of four weeks, and then persisted with slight variation up to admission. She first noticed difficulty in getting upstairs, then inability to hold objects in her hands, and to raise her arms above her head, then difficulty in sitting up and holding her head erect. Drooping of the eyelids, inability to close the eyes tightly, inability to smile, difficulty in chewing and swallowing, and inability to speak clearly were also complained of. All symptoms were made worse by voluntary action.

On examination, patient showed the typical myasthenic facies, with much facial weakness, extreme weakness of the jaw movements and considerable weakness of all the limb muscles, greater proximally, and also of the neck and trunk muscles. She could not climb stairs, and she had to be helped out of bed.

She was discharged to a convalescent home on October 30, 1932, and remained in the same condition until May 5, 1933, when, following the administration of ephedrine mg. 32 three times daily, she became much better. The improvement was evident on examination, and when the ephedrine was stopped for seven days, at the time of the biopsy on February 24, 1934, there resulted a considerable increase in the weakness of the trunk and limbs.

Case of Muscular Weakness associated with Graves' Disease.

F. P., male, aged 39, was admitted to the National Hospital, under Dr. Carmichael, on May 1, 1934. Three weeks before admission he began to complain of general weakness and exhaustion, and also of occasional nausea and vomiting and loss of weight. His arms felt weak and heavy and he was only able to walk 100 yards. On admission the pulse-rate was 124 per minute, and the blood-pressure 140/60. There was slight fullness of the neck in the thyroid region, fine tremor of outstretched hands and a slight degree of exophthalmos. There was some weakness of opening of the jaw against resistance, some weakness of eye closure and considerable reduction in muscle strength in all movements in the arms and legs.

Case of Periodic Muscular Weakness.

C. H., male, aged 33, has been a patient at the National Hospital, under the care of Dr. Symonds, since February 4, 1927. At the age of 6 years it was noticed that he could not run and play with other boys, and that he stumbled as he walked. From this time he began to complain of periods of general muscular weakness, which would come on suddenly, last for three or four weeks, and then gradually improve. These attacks recurred at intervals of several months, and he is certain that up to the age of 17 he recovered his

strength between the attacks. At this age he commenced heavy work as a butcher, since when he has complained of some general weakness between the attacks, which is always relieved by complete rest from work. During an attack his arms become very weak, and he is not able to carry 6 lb., whereas usually in his work he carries 60 lb. with ease. Also his legs become very weak, and he has great difficulty in getting upstairs.

On examination at a time when the patient felt well there were found slight bilateral ptosis and slight weakness of eye closure. The proximal muscles in the arms and legs were somewhat thinner than the distal muscles, but there was no localized wasting. The strength was generally diminished in the muscles of the arms and legs, more proximally and especially in the deltoid muscles. There was slight hypotonia in the arms and legs. The deep reflexes were all present and equal, but diminished. In the erect posture he stood with considerable lordosis but he rose quickly from the supine position, and had no difficulty in getting upstairs.

A sister of the patient is similarly affected.

The biopsy was performed on March 26, 1934, towards the end of a period of increased weakness.

Pseudohypertrophic Muscular Dystrophy.

Case 1.—P. H., male, aged 14, was admitted to the National Hospital under Dr. Hinds Howell, on November 11, 1933. He was a healthy child until at the age of 6 he began to complain of difficulty in getting upstairs, of rising from the supine position and in running. This weakness gradually progressed in his legs and trunk and affected his arms, so that since the age of 11 he has not been able to stand or walk, but he can still use his arms to feed and wash himself.

On examination there was found extensive wasting of the pectoralis major, the glutei, and the muscles of the arm, back and thigh. Pseudohypertrophy was present in both calves. The strength was extremely weak in all movements.

Case 2.—V. H., male, aged 12, brother of Case 1, was admitted to the National Hospital, under Dr. Hinds Howell, on November 4, 1933.

It is not necessary to describe this case, as the symptoms and progress of the disease and the condition on examination were similar to Case 1.

Case of Muscular Atrophy Secondary to Nerve Degeneration.

J. S., male, aged 69, was admitted to the National Hospital, under Dr. Collier, in January, 1934. Seven years before admission patient began to complain of weakness of his right foot. This slowly progressed and affected the whole leg, and for three years he had had to walk with a stick.

On examination it was found that the right foot was dropped, and that there was considerable wasting of the right anterior tibial muscles, the calf muscles and to a less extent the thigh muscles. All movements at the right

ankle were extremely weak, and those at the right leg and knee noticeably weak. The biceps, knee and ankle jerks were absent in both limbs.

Histological examination of excised muscle showed a condition of simple muscle atrophy of long standing secondary to neural degeneration.

Case of Dystrophia Myotonica.

G. F., male, aged 64, was admitted to the National Hospital, under Dr. Carmichael, on November 2, 1933.

At the age of 27, he began to complain of difficulty in relaxing his grasp in both hands, and at the age of 36, of weakness in his arms and legs, which has gradually progressed. He now has difficulty in walking 100 yards without resting. Weakness of the neck muscles, and slow relaxation of the face muscles after smiling or closing his eyes, have also been complained of.

On examination there was found a myopathic facies, weakness and wasting of the sternomastoids and of the arm and leg muscles generally, with pronounced myotonia in the flexors of the wrist and fingers, and mechanical myotonia in the muscles of the tongue, forearm, thenar eminence, and calf.

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THE VENOUS SYSTEM OF THE VELUM INTERPOSITUM OF THE RHESUS MONKEY AND THE EFFECT OF EXPERIMENTAL OCCLUSION OF THE GREAT VEIN OF GALEN.

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In an earlier paper [1] an account has been given of a series of experiments on dogs in which the great vein of Galen was occluded at various points on its course to determine if hydrocephalus would develop. Although the animals were allowed to survive for three months none was found at autopsy to have developed this condition. The venous system of the velum interpositum of the dog was also investigated and it was found to differ from that of man. In view of the fact that the effects of experimental occlusion of the great vein of Galen have so far been investigated in no animal other than the dog, it was decided to repeat these experiments using the rhesus monkey. It was hoped to find in the rhesus monkey a Galenic system which resembles more closely that of man. These monkeys are relatively cheap to purchase and they can be kept in good health under laboratory conditions. It is proposed to consider: (1) The anatomy of the Galenic system of the rhesus monkey; (2) the effects which follow experimental occlusion of the great vein of Galen.

(1) THE ANATOMY OF THE GALENIC SYSTEM OF THE RHESUS MONKEY.

A careful search through the relevant literature has failed to reveal any account dealing with the anatomy of this venous system. For the purposes of this part of the investigation three rhesus monkeys were used. The findings in these animals were extended and supplemented by observations made on the brains of animals in which the great vein of Galen had been occluded experimentally.

Method.—The animals were anaesthetized and cannulae were placed in both internal carotid arteries and also in both internal jugular veins. The rhesus monkey, unlike the dog, has large internal jugular veins. The head, with the cannulae in position, was severed from the body and washed free from blood by injecting warm normal saline solution through

both internal carotid arteries. When the washings were no longer blood-stained, carmine gelatine was injected through both internal jugular veins until the conjunctivæ were found to be coloured. The whole head was then placed in cold running water and allowed to cool as rapidly as possible. When cold, the cranium was opened and the brain fixed in situ in 5 per cent. formol saline solution. If care is taken to discontinue

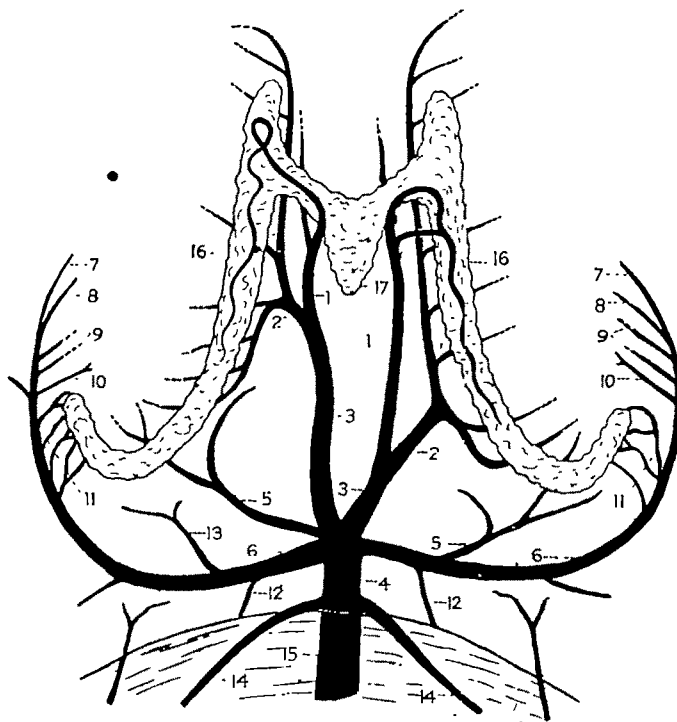


FIG. 1.—Semi-diagrammatic representation of the veins of the velum interpositum and their main communications in the rhesus monkey (control No. 1). In this instance the mode of termination of the basilar veins resembles that found in man. The true relations of the various structures have been distorted and the vessels are depicted as occupying one plane: 1, Vein of choroid plexus; 2, vein of corpus striatum; 3, vein of Galen; 4, great vein of Galen; 5, epithalamic vein; 6, basilar vein; 7, anterior cerebral vein; 8, sylvian vein; 9, striate tributaries of basilar vein; 10, pituitary veins; 11, choroidal tributaries of basilar vein; 12, cerebellar tributary of basilar vein; 13, tributaries from the midbrain to basilar vein; 14, veins from occipital cortex to great vein of Galen; 15, straight sinus; 16, choroid plexus of lateral ventricle; 17, choroid plexus of third ventricle.

the carmine gelatine injection as soon as the conjunctivæ become coloured the mass can frequently be restricted to the venous system. After fixation the brains were dissected in the ordinary way.

One of the most striking features of the Galenic system of the rhesus monkey is its remarkable irregularity. Not only does the arrangement

of the vessels vary from animal to animal but the system is often unbalanced, the one side differing markedly from the other. The Galenic system of the rhesus monkey seems to be even more variable than that of the dog. Fig. 1 is a semi-diagrammatic representation of the Galenic system of the first brain to be examined. The vein of the choroid plexus is a well-defined vessel which receives blood from the choroid plexus of the lateral ventricle and also from that of the third ventricle. Soon after leaving the choroid plexus it is joined by a tributary which receives blood from the anterior part of the corpus striatum. Occasionally this vessel is as large or even larger than the vein of the choroid plexus. After pursuing a course backwards through the velum interpositum for a distance which varies considerably in different brains, the vein of the choroid plexus unites with the vein of the corpus striatum to form the vein of Galen. In one specimen the vein of the choroid plexus failed to join the vein of the corpus striatum and both these vessels terminated separately in the great vein of Galen. The vein of the corpus striatum is a well-defined vessel and is considerably larger than the vein of the choroid plexus. No communications seem to exist between its tributaries and the venous system of the choroid plexus. The veins of Galen run backwards until they reach the region of the splenium of the corpus callosum where, under ordinary circumstances, they unite to form the great vein of Galen. This latter vessel turns upwards round the splenium and ends by becoming the straight sinus at the anterior border of the tentorium cerebelli.

In one instance the veins of Galen did not unite but maintained their individuality until they terminated in the straight sinus. In this animal there was no great vein of Galen. Two pairs of tributaries are usually received by the great vein of Galen near its origin. The first drains blood mainly from the pulvinar but also from the dorsal end of the optic tract, the superior colliculus and the posterior part of the caudate nucleus. A few tributaries may be received from the choroid plexus of the lateral ventricle, but if they exist at all they are very small and of little consequence compared with the vein of the choroid plexus and the choroidal tributaries of the basilar vein. This vessel as already stated usually terminates in the great vein of Galen near its point of origin, but the following variations have been encountered. It has been observed to end in: (1) The vein of Galen; (2) the basilar vein; (3) the under surface of the great vein of Galen close to the point where it becomes the straight sinus. As this vessel appears to drain blood mainly from the surface of the posterior part of the optic thalamus it is proposed to refer to it as the epithalamic vein.

The next pair of vessels to join the great vein of Galen is the basilar veins. From a consideration of fig. 1 it will be observed that in this particular animal the basilar veins resemble very closely those of man. The basilar vein is formed by the union of the anterior cerebral vein and the Sylvian vein. It courses backwards and inwards round the mid-brain, where it is situated below the optic tracts and terminates in

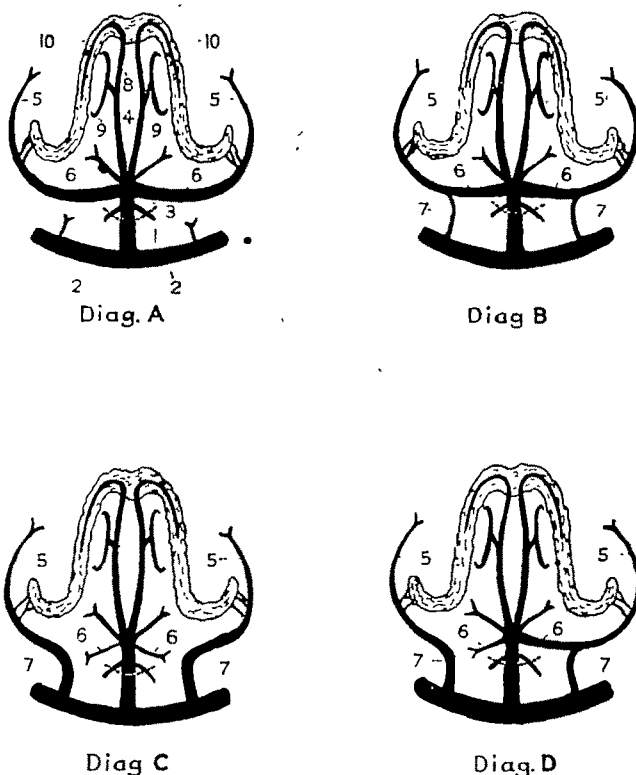


FIG. 2.—Diagrams illustrating variations in the mode of termination of the basilar vein : 1, Straight sinus ; 2, lateral sinus ; 3, great vein of Galen ; 4, vein of Galen ; 5, prebasilar vein ; 6, superior postbasilar vein ; 7, inferior postbasilar vein ; 8, vein of choroid plexus ; 9, vein of corpus striatum ; 10, choroid plexus of lateral ventricle.

the beginning of the great vein of Galen. It receives the following tributaries: (1) A few striate veins near its origin; (2) pituitary veins; (3) inferior choroidal veins from the choroid plexus of the descending horn; (4) numerous vessels from the optic tract and the neighbouring structures; (5) venules from the mid-brain; (6) a few small veins from the superior surface of the cerebellum. A basilar vein of this type was, however, discovered in no other animal. In all the remaining eleven

brains which came to be examined and which included two from control animals and nine from animals in which the great vein of Galen had been occluded experimentally, the basilar vein was found to terminate in a different manner. Some of the various modes of termination of the basilar vein which have been encountered are indicated in fig. 2. Diagram C is a representation of the mode of termination of the basilar vein in the second control animal. It will be observed that here the basilar vein corresponds with that of the first control animal (diagram A) until it reaches the lateral aspect of the mid-brain, when it turns first sharply downwards and then backwards and slightly outwards into the tentorium cerebelli and terminates in the lateral sinus. In this animal the termination of the basilar vein in the great vein of Galen is represented by a small venule which has no direct communication with the more anterior part of the vein. It is probable, however, that communications of a capillary nature are present. The third control animal (diagram B) was found to possess a basilar vein which was not unlike that of the first control in so far as the main flow of blood was into the Galenic system, although a small amount of blood passed directly into the lateral sinus.

For convenience it is proposed to describe by the term "prebasilar vein" that portion of the basilar vein which extends from the point of origin to the lateral aspect of the mid-brain. That portion of the vein which continues from the mid-brain in the tentorium cerebelli to the lateral sinus will be termed the "inferior postbasilar vein," and the vessel which occupies a position which corresponds with the terminal portion of the basilar vein as depicted in diagram A will be described as the "superior postbasilar vein."

The prebasilar vein was constant in all the brains examined, while the superior and the inferior postbasilar veins were variable. It is noteworthy that the inferior postbasilar vein just before entering the tentorium cerebelli receives a number of venules from the anterior aspect of the pons and a well-defined venule from the external geniculate body.

When the brains of the monkeys in which the great vein of Galen had been occluded came to be examined it was discovered that the most frequent arrangement was of the type in which the superior postbasilar vein was very small and had only very feeble or no connections at all with the prebasilar vein, while the inferior postbasilar vein was a large vessel which received the whole of the blood from the prebasilar vein. This was the condition found in the second control animal and is

indicated in diagram C. Occasionally there was a more definite communication between the superior postbasilar vein and the prebasilar vein, but the main flow of blood was almost invariably into the inferior postbasilar vein. In the only exception (diagram D) the superior and the inferior postbasilar veins on the right side received an equal amount of blood from the prebasilar vein, although on the left side the superior postbasilar vein was represented by a minute venule. It was not uncommon to discover a different arrangement on the two sides. It is noteworthy that a main blood flow into the superior postbasilar vein was not found in any of the animals in which the great vein of Galen had been obstructed.

Exception may perhaps be taken to the use, for the purpose of determining normal anatomy, of material derived from animals in which the great vein of Galen had been experimentally occluded, and it may be claimed that the constant presence of a large inferior postbasilar vein in all these animals was due to the post-operative dilatation of small pre-existing communications. It may also be contended that the presence of a small superior postbasilar vein was merely a result of disuse following the occlusion either of the termination of the vessel itself or of the great vein of Galen into which it drains. Although one cannot entirely exclude these possibilities they would appear to be most improbable for the following reasons: (1) As will be pointed out later no evidence could be obtained that the basilar vein takes a special part in the formation of collateral circulation after occlusion of the great vein of Galen in the rhesus monkey; (2) in no instance did any form of spreading thrombosis follow obstruction of the great vein of Galen. In nearly every instance the vessels remained patent almost directly up to the occluding clip. If a large superior postbasilar vein had existed previous to operation it would almost certainly have remained patent and in the brain prepared for dissection it would have been found to contain injection mass; (3) if a small superior postbasilar vein were merely an expression of disuse following obstruction either of the termination of the vein itself or of the great vein of Galen into which it drains, it is difficult to understand why that portion of the vein which joins the great vein of Galen should nearly always have been found to be present, while in many instances it had no obvious connection with the prebasilar vein; (4) two of the brains were obtained from animals in which death had occurred only two days after operation; (5) finally, in one of the three control animals the superior postbasilar vein was represented by a small venule which had no direct communication with

the prebasilar vein, while the inferior postbasilar vein was represented by a large vessel which received the whole of the blood from the prebasilar vein.

The great vein of Galen is joined on its upper surface by one or more venules from the under surface of the corpus callosum, and at the point where it terminates by becoming the straight sinus it is joined by two large veins which drain blood from the under surface of the occipital lobes. In the rhesus monkey the lower border of the falx cerebri contains the inferior longitudinal sinus.

To sum up, it would appear that although the Galenic system of the rhesus monkey may bear at times a fairly close resemblance to that of man, this is not the usual finding. It has been shown that in the specimens examined the basilar vein terminated most frequently in the lateral sinus. In this respect the system resembles that of the dog where this mode of termination of the basilar vein is a constant finding.

The vein of the corpus striatum of the rhesus monkey is characterized by its relatively large size and the extensive area from which it receives blood. Very little blood seems to leave the corpus striatum through the striate tributaries of the prebasilar vein.

With regard to the venous return of the choroid plexus of the lateral ventricle, the bulk of the blood escapes through the vein of the choroid plexus. Some blood also passes from the choroid plexus of the descending horn into the prebasilar vein. It is possible that a few venules connect the choroid plexus with the epithalamic vein. The plexus-like nature of the whole of the venous system of the velum interpositum must however be borne in mind and it is conceivable that communications exist which may escape detection on ordinary examination.

(2) THE EFFECT OF EXPERIMENTAL OCCLUSION OF THE GREAT VEIN OF GALEN IN THE RHESUS MONKEY.

The animals varied in age from about two to three years. With one exception they were all males.

Operative procedure.—Anæsthesia was first obtained with ether. Chloralose in a proportion of 0.1 grm. per kilo of body-weight was then injected intravenously and the administration of the ether discontinued. The anæsthesia was maintained by the chloralose. Except for two details the operative procedure was identical with that employed previously for the dog and which has been described in an earlier paper [1]. It was the custom to give the monkeys hypertonic saline solution

intravenously just before opening the cranium so as to obtain a shrinkage of the brain, and after operation a quantity of normal saline solution was injected into the peritoneal cavity. The volume of solution injected into the peritoneal cavity was determined by the amount of blood which had been lost during the operation. By employing this procedure it was found that the convalescent period was considerably shortened. An experiment was deemed successful when after occlusion of the great vein of Galen the animal maintained good health until six weeks later when it was killed.

The venous system of all the brains was injected with carmine gelatine as it was important to determine in each instance the precise anatomy of the Galenic system and if possible the mode of collateral circulation formation. The subsequent treatment of the brains was the same as that which was employed for the dogs' brains in the investigation to which reference has already been made.

ANATOMICAL CHANGES FOLLOWING OCCLUSION OF THE GREAT VEIN OF GALEN.

The great vein of Galen was occluded in nine monkeys. In two of these death occurred as a direct consequence of operation after two days, and two animals died suddenly in convulsions after a normal survival period of fourteen days. In five instances the monkeys were maintained in good health for six weeks. These were regarded as successful experiments.

None of the animals in which the great vein of Galen had been occluded was found to have developed hydrocephalus, and in most instances the ventricles appeared to be somewhat collapsed. The relatively short course of the great vein of Galen in the rhesus monkey did not permit of much variation in the placing of the occluding clip. In almost every instance the vessels remained patent close up to the fibrous capsule which had formed round the clip. In three of the successful cases the clip had been placed on the termination of the great vein of Galen. In these cases the termination of the superior postbasilar vein in the great vein of Galen remained patent. In one instance the clip was placed on the middle of the trunk and in another on the anterior part of the great vein of Galen. In both these cases the termination of the superior postbasilar vein was occluded.

One of the most striking features of the Galenic system of the rhesus monkey after occlusion of the great vein of Galen was the entire absence of any clear indication of the manner in which collateral circulation had

developed. Except for the presence of the occluding clip, the whole system appeared to be normal. In the three instances in which the termination of the superior postbasilar vein had remained free from obstruction, there was no clear indication that this vessel had taken a special part in the formation of collateral circulation. Similarly the apparently normal appearance of the choroidal tributaries of the prebasilar vein made it seem doubtful if they had served as the route by which the obstructed blood had escaped. The choroid plexuses remained normal to naked-eye inspection. Unfortunately the method employed for preparing the brains prevented rapid fixation of the choroid plexuses, and they were rendered unsuitable for histological examination. The Galenic systems of the four monkeys which failed to survive six weeks also presented nothing of note. No explanation could be found for the onset of fatal convulsions in two of the monkeys.

To recapitulate, it would appear that obstruction of the great vein of Galen in the rhesus monkey, as in the dog, is not followed by hydrocephalus. In the case of the monkey, however, no clear evidence of the formation of collateral circulation could be discovered. The choroid plexuses remained unchanged in their gross appearance.

DISCUSSION.

As a result of the above experiments it may be concluded that under ordinary circumstances a degree of venous obstruction comparable to that which may be expected to follow occlusion of the great vein of Galen in man can only be obtained in the rhesus monkey by the simultaneous occlusion of the great vein of Galen and of the inferior postbasilar vein. Occlusion of the inferior postbasilar vein would present considerable experimental difficulty, for it would be desirable to occlude the vessel without injury to the lateral sinus.

On the other hand it is noteworthy that it was found impossible to discover in what way blood had escaped from the choroid plexuses in the animals in which the great vein of Galen had been occluded. Unlike what obtains in the dog the route through the choroidal tributaries of the prebasilar vein did not appear to have been specially utilized.

It is also important to bear in mind that not only must the route of escape of the blood from the choroid plexuses be considered, but also that of the blood from the greater part of the corpus striatum. It is possible that there is no main channel through which collateral circulation is established, but that the escape of blood is a general process

through the communications of the minute tributaries of the occluded vessels with those of the veins of neighbouring systems. This aspect of the subject requires further investigation.

Since this work was originally undertaken, Dandy [2] has published in book-form an account of his experiences with benign tumours of the third ventricle. This worker obviously regards ligation either of the veins of Galen or of the great vein of Galen as a dangerous procedure and speaking of pineal tumours he says "their operative removal is a far more difficult problem because they are with few exceptions firmly embedded and the veins of Galen both large and small usually pass through the tumour, practically precluding in such instances a successful removal." Unfortunately Dandy does not state whether in any of his cases the tumour interfered with the blood return through these vessels. From a consideration of his description of the findings at operation, it would seem probable that a degree of obstruction to the veins of Galen may have been present in a number of the cases. Dandy's reluctance to divide either the veins of Galen or the great vein of Galen is presumably based on the belief that hydrocephalus or a state of increased intracranial pressure may follow such a procedure. It is noteworthy, however, that in referring to the increased intracranial pressure which is associated with tumours of the third ventricle he states that this condition "was due solely to the obstruction to the pathways through which cerebrospinal fluid finds its exit from the cerebral ventricles." In two cases he was compelled to divide one of the veins of Galen, in another both veins of Galen "had to be doubly clipped and divided." It is significant that no untoward symptoms are reported to have arisen as a result of this procedure in any of these cases.

SUMMARY.

(1) The arrangement and communications of the venous system of the velum interpositum of the rhesus monkey are described. The system is characterized by its extraordinary variability. Although on rare occasions it may bear a fairly close resemblance to that of man this is not the usual finding. The chief difference is in the termination of the basilar vein. This vessel may terminate in the great vein of Galen, but most frequently the greater part of its blood is diverted directly into the lateral sinus.

(2) The great vein of Galen was successfully occluded in five monkeys. None of these animals was found to have developed hydro-

cephalus after a survival period of six weeks. The choroid plexuses appeared normal to naked-eye inspection. A basilar vein of the human type was found in none of the experimental animals. No clear evidence could be obtained of the way in which the collateral circulation had developed. It is suggested that blood may perhaps have escaped through the communications of the minute tributaries of the occluded vessels with those of neighbouring systems.

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AUTONOMIC CONTROL OF THE URINARY BLADDER.

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INTRODUCTION.

BEFORE continuing our experiments dealing with the encephalic control of micturition, the first portion of which has already been published (Langworthy and Kolb, 1933), we appreciated the necessity for more exact information concerning the function of the autonomic nerve supply. These observations were to be made upon the same experimental animal, the cat, and were to employ as far as possible the same technical methods. The study of the sympathetic division of the autonomic innervation of the bladder promised to be of particular interest because of Learmonth's suggestion (1931) that a presacral neurectomy might be performed to improve bladder function in case of injury preventing the complete emptying of the viscus.

Animal experimentation offers opportunities for an investigation of the autonomic nervous system not available in clinical work. Denny-Brown and Robertson (1933, B) in their recent study of bladder activity following lesions of the cauda equina and spinal cord were forced from a lack of available material to neglect the function of the intact sympathetic fibres, a function which probably has an important rôle in the explanation of their findings. On the other hand, of course, the experimentalist must base his observations on different objective criteria from those of the clinician. In the animal it is obviously difficult to study the residual urine remaining after micturition; but under anæsthesia it has been shown that the bladder of the individual experimental animal empties on a volume which is remarkably constant. With the preparation under light ether anæsthesia, the present experiments therefore record the volume required for reflex micturition and measure the bladder pressure following the introduction of fluid increments. Moreover, they indicate the amount of fluid held in the bladder under constant pressure.

It may be objected that these mammalian findings are not immediately

applicable to the study of micturition in man. Elliott (1907) indeed states that he could obtain changes in bladder pressure and volume on stimulation of the sympathetics in the cat, but not in certain other mammals even of closely related species. The authors have not extended their studies of bladder inhibition to other forms. From the observations on the bladder of normal human beings, made by Denny-Brown and Robertson (1933 A), it is quite clear that inhibition plays an important rôle. Furthermore, from the standpoint of comparative physiology, one certainly would expect that the same general mechanism of inhibition of bladder activity would be operative in all mammalian forms even though this inhibitory activity was better developed in some animals than in others. While Learmonth's experiments on the sympathetic nerves of the bladder in man and ours upon cats employed such different criteria and technique that they cannot be compared directly, nevertheless they bring out much the same essential facts in reference to the sympathetic innervation.

METHODS.

Sixty-one female cats were used as experimental preparations. They were kept under light ether anæsthesia during the operations and subsequent observations of bladder activity.

The apparatus was an amplification of the one employed in previous experiments (Langworthy and Kolb, 1933). A fine glass catheter was inserted into the bladder through the urethra, and the free end attached to the recording apparatus. The catheter was not tied into the bladder, but held in place by the tone of the urethra and sphincters. When reflex micturition began, fluid escaped from the catheter, which became loose in the urethra. The insertion of the catheter without tying prevented the bladder from becoming distended beyond the physiological limits of the experiment.

By means of a three-way tube, the catheter, an open-end manometer of 3 mm. bore, and a burette graduated to $\frac{1}{10}$ c.c. were connected. From the burette water warmed to body temperature could be introduced into the bladder at the rate of about 1 c.c. per minute. Readings were taken after the addition of each 5 c.c. In most of the observations, and especially when the bladder was unusually irritable, the flow was stopped at each 5 c.c. in order that the lowest possible readings could be obtained.

After the introduction of equal increments of fluid, it was possible with such an arrangement of the apparatus to determine not only the

fluid pressure in the bladder during filling and at the time of sphincter relaxation, but also the volume of fluid necessary for the stimulation of micturition. Later, in connection particularly with stimulation of the sympathetic fibres, the importance of determining bladder volume under constant pressure became evident. In order that fluid might enter or leave the bladder freely, an apparatus for such determinations was required to have but little inertia. The simple apparatus that was adopted is shown in the diagram in fig. 1. Removal of the pinch-cock introduced it at once into the fluid circuit previously described.

By means of heavy rubber tubing a large open reservoir was attached to the bottom of one of two 100-c.c. burettes. These were connected across the top by rubber tubing in which was inserted, by means of a

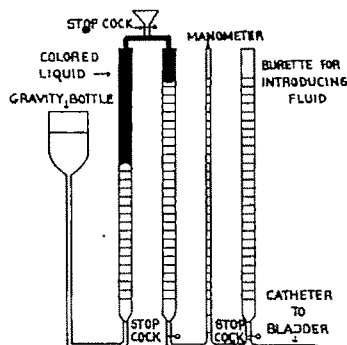


Fig. 1

FIG. 1.—This diagram demonstrates the apparatus used to measure the intravesical pressure after adding equal increments of volume and also to observe the volume of the bladder at constant pressures. A full description is given in the text.

three-way tube, a funnel which could be closed off by a stop-cock. Rubber tubing also served to connect the bottom of the second burette into the system with the manometer and the catheter to the bladder. If constant pressure readings were not desired, this apparatus could be shut off from the remainder of the circuit by means of a pinch-cock on the tubing.

In order to maintain exact pressure readings, a gravity bottle of large diameter and fluid capacity was required. Then by raising or lowering the bottle one could set the bladder pressure at a constant, as indicated by the manometer. Before readings were taken, the constant pressure apparatus was filled carefully with water until no bubbles of air remained. Following this, kerosene stained with Sudan III was introduced at the

top of the burettes from the funnel connecting the tubing until it filled approximately one-half of the burette nearest the gravity bottle and extended to the upper level of the graduations in the second burette. Both tubes were graduated to two-tenths of a cubic centimetre. The coloured fluid acted as an indicator. In later experiments chloroform was added to the kerosene drop by drop until the mixture was almost the same specific gravity as water. With the indicating fluid and the water of similar weights, the constancy of the pressure readings was held more perfectly. Determinations with this apparatus were always begun with the bladder empty. The pressure was then raised and the volume of fluid running in or out of the bladder was subsequently measured on one or the other of the two burettes, depending upon the position of the meniscus, which changed with the direction of the flow of the water. This apparatus, an adaptation of one used by Mortensen and Weed (1934) in their study of the cerebrospinal fluid, was found satisfactory for the present work.

A COMPARISON OF READINGS WITH THE PRESSURE OR VOLUME CONTROLLED.

Two graphs in the second figure illustrate the complementary pictures obtained when either the volume or the pressure of the bladder contents are increased in equal increments and the other factor determined. In order to simplify the diagram a sympathectomized preparation with a small bladder and low-pressure readings was used.

Thus in Graph A increments of volume are indicated on the ordinates and the pressures on the abscissæ. The initial pressure with the bladder empty was 0.8 cm. of water. With the addition of fluid the pressure readings remained below 4 cm. until 20 c.c. had entered the bladder. The pressure then rose gradually until the sphincters relaxed reflexly upon 28.5 c.c. of fluid at a pressure of 52 cm. The bladder was then connected with the apparatus for recording bladder volumes at constant pressures.

The results of this second determination are illustrated in Graph B in which the increments of pressure are recorded on the ordinates and the volume of the bladder on the abscissæ. When the pressure was set at zero or one centimetre, no fluid entered the bladder. This was to be expected because in the previous graph the lowest pressure recorded with fluid in the bladder was 1.8 cm. When the pressure was raised to 2 cm. the bladder held 4 c.c., and 14.8 c.c. with the pressure at 3 cm. The bladder contained 20.3 c.c. when the pressure was set at 4 cm.

This gives a very accurate check of the previous pressure readings and illustrates the important fact that the bladder will fill to a great portion of its capacity at a low pressure. With the addition of the next 3 cm. of pressure, there was a small increase in the bladder volume so that at 7 cm. of pressure the bladder held 25.2 c.c., or only 3 c.c. less than the amount required in Graph A to induce reflex micturition. Thereafter the character of the volume increments in the bladder changed markedly. With the addition of further increments of pressure, the volume increase was small and almost a constant factor. In order not

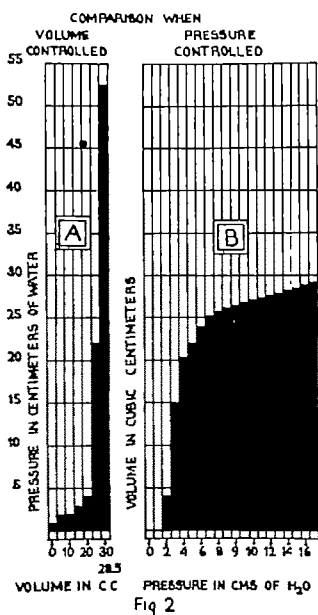


Fig 2

FIG. 2.—Diagram A shows the pressure in a bladder after adding equal increments of fluid, and diagram B the volume of the same bladder when the pressure was increased by equal increments.

to damage the preparation for further study, this experiment was not carried beyond the normal volume required for micturition. At a pressure of 17 cm. the bladder held 28.8 c.c., an amount which had produced reflex micturition in the previous diagram. When the controlled pressure was raised slowly, reflex micturition did not occur at this volume.

Except at the end, when the bladder was filled, the two graphs are complementary. At this time a pressure rise with sphincter relaxation is shown occurring in fig. 2 A, while fig. 2 B shows the volume

increasing by small and fairly equal gradients as the pressure was increased by 1 cm. gradients. The bladder at this stage followed the law of elastic membranes. It did not follow this law of elastic membranes, however, until the bladder had been filled with more than 25 c.c. of fluid. Previous to this time its responses were determined by the smooth muscle in the wall of the hollow organ.

Had the pressure been increased by larger gradients, the bladder would have reached its reflex micturition volume and emptied. Indeed when the pressure was set at a high point such as 25 cm. of water, the bladder would alternately fill and empty an indefinite number of times.

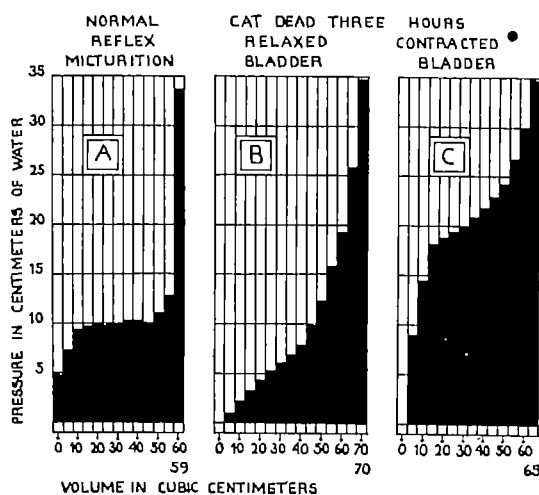


Fig 3

FIG. 3.—Diagram A gives the intravesical pressure of a normal bladder after the addition of increments of volume, and diagram B the pressure in the same bladder with the muscle relaxed three hours after removal of the bladder from the body. The reading in diagram C was made when the muscle of the incised bladder was tightly contracted.

In the present case the very slow raising of the pressure defeats the normal reflex of micturition. Micturition is initiated by waves of bladder contraction which finally become fused in a constant tonic contraction. When the pressure is held constant at a low level these waves are suppressed and are unable to break through to initiate the emptying reflex.

Figure 3 shows the pressures after the addition of equal fluid increments to the normal cat's bladder under dial anæsthesia (Graph A). The pressure readings were extremely constant, as they are with this type of anæsthetic, and until the bladder was nearly filled remained

around 10 cm. of water. Thereafter the pressure rose and the bladder emptied reflexly at a pressure of 33.7 cm. and a volume capacity of 59 c.c. The cat was killed, the bladder removed from the body, a catheter tied in the urethra and the organ placed in warm saline solution. Three hours after the removal of the bladder, another reading was made; the muscle at that time was relaxed and the pressure readings after the addition of fluid are recorded in Graph B. With the addition of the fluid increments, the bladder pressure rose by fairly equal increments until the bladder was almost completely filled. After reaching the reflex emptying point of the normal animal, the pressure rises became progressively greater. The bladder was obviously near the limits of capacity at 55 c.c.

The smooth muscle of the bladder wall was still responsive, a strong contraction occurring when the fluid was expressed through the catheter. The viscus then was tightly contracted; a reading was made which is recorded in Graph C. When the first increments of water were introduced, the pressure rose steeply, but as the bladder became distended with fluid these rises became smaller, so that they resembled the rises recorded for the relaxed bladder in Graph B. After the bladder became distended to that volume effecting micturition reflexly, the increments of pressure-rise again increased in size.

These charts show that pressure in the dying bladder increases by graded increments, and there is, moreover, a loss of that adaptation by which increasing amounts of fluid are held at approximately the same pressure. The suggestion will be made later in this paper that Graph B of the relaxed bladder resembles the bladder musculature behaviour following sympathectomy, and Graph C of the contracted bladder has some resemblances to the condition observed after parasympathectomy.

These graphs also indicate that the bladder has a size which is relatively constant for the individual, and that reflex micturition under anaesthesia occurs when this volume is reached. The bladder volume is not at once diminished by section of the sympathetic nerves, but on the contrary the reduction is gradual. Similarly the bladder does not immediately expand because of the loss of tone resulting from section of the parasympathetic innervation. In this case the wall is probably stretched passively by the accumulation of fluid which it cannot expel. Similarly, the dead bladder shows approximately the same volume as does the live, and when this volume is reached or exceeded the pressure rises markedly with further addition of fluid.

STIMULATION OF THE SYMPATHETICS.

Following sympathetic stimulation in the cat, Elliott (1907) reported inhibition expressed as either a decreased bladder pressure or an increased bladder volume. This was one of the few convincing reports in the literature. Inasmuch as his findings were not expressed in terms of the technique of the present work, the stimulation was repeated in many of our experiments. This supplied new information concerning the changes in bladder pressure or volume which could be obtained at

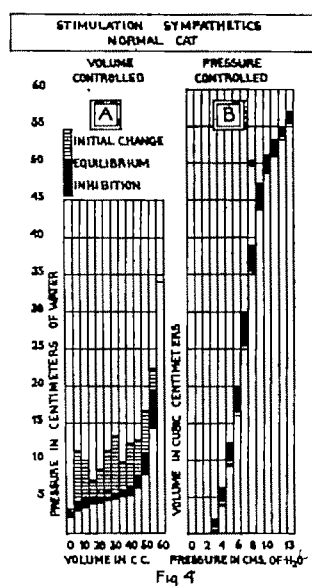


FIG. 4.—Graph A shows the effect of stimulation of the sympathetics upon the pressure of fluid in the bladder of the normal cat at different stages of filling: Graph B demonstrates the change in volume of the vesical contents on sympathetic stimulation. The initial effect of stimulation is indicated by the cross-hatched area and the relaxation by the black rectangle. The line between indicates the reading before stimulation.

different stages in the filling of the viscus. The current was supplied by means of a simple Harvard inductorium connected to a shield electrode which caught together the sympathetic fibres of the two sides. The construction of the electrode prevented the escape of current to adjacent structures. At first the hypogastric nerves were freed and caught in the electrode, but later on it was found more satisfactory to include both sympathetic trunks just above the emergence of the hypogastric nerves. The pressure changes were recorded after the addition of 5 c.c. fluid increments, and again after increasing increments of

pressure were applied to the bladder contents. The two types of results are shown in Graphs A and B in fig. 4.

After the fluid increments had been added to the bladder, the pressure was allowed to fall to the lowest level possible, and then this pressure was recorded. In every case stimulation of the sympathetics at this time caused a quick and non-sustained rise of bladder pressure followed by a fall below the lowest reading obtained before stimulation. This fall was slow and the relaxation occurred after a definite latent period which was occupied partially by the initial contraction. When the stimulus was removed, the pressure rose slowly, and after fifty seconds reached the point recorded before stimulation. In Graph A the middle line or the upper level of the black rectangle represents the lowest pressure recorded before stimulation, the cross-hatched area above shows the height of the initial rise and the black rectangle the fall of bladder-pressure which followed the stimulation.

The intravesical pressure of the empty bladder was recorded at 2.2 cm. (fig. 4, Graph A). Stimulation of the sympathetics elevated the pressure to 3.1 cm.; no relaxation could ever be demonstrated with the bladder empty. The addition of 5 c.c. of fluid raised the bladder pressure to 4 cm. of water. Sympathetic stimulation at this time elevated the pressure to 11.2 cm., and then lowered it to 3.3 cm. Until more than 30 c.c. of fluid had been introduced, the pressure of water in the bladder remained between 4 and 5.1 cm. Throughout this phase of the experiment the rises following sympathetic stimulation showed variations of no particular significance. As the fluid volume was increased, the relaxation, on the other hand, tended to become less marked. When, however, it is realized that the bladder before stimulation is holding an increasing quantity of fluid at approximately the same pressure, then the occurrence of such a tendency might well be expected.

Elevation of the bladder volume to 40 c.c. effected a rise in pressure to 6.2 cm., and stimulation increased the amplitude of relaxation to 0.8 cm. Then, with the increasing fluid volume in the bladder and the higher manometer readings, the amount of pressure fall obtained increased markedly, so that it was not a fraction of a centimetre, but instead several centimetres. Indeed, with 50 c.c. of fluid in the bladder, the relaxation amounted to 5 cm. The bladder emptied reflexly on 60 c.c. at a pressure of 34 cm. As far as the pressure readings are concerned, the inhibitory effect of sympathetic stimulation becomes vastly greater as the bladder is approaching the limits of its capacity. As the bladder

becomes distended, the initial rises become somewhat smaller; these rises on sympathetic stimulation never caused fluid to escape from the urethra.

We turn now to the complementary picture showing the volume changes on sympathetic stimulation with the pressure increased by one centimetre increments. These readings were made on the same preparation as those charted in Graph A (fig. 4). In Graph B the middle line at the lower edge of the black rectangle represents the normal reading, the bladder volume before stimulation occurred. The cross-hatched block indicates the fluid which ran out of the bladder at the beginning of stimulation, while the solid black area signifies that volume of fluid entering when relaxation occurred. As would be expected, fluid failed to enter the bladder at 1 or 2 cm. of pressure, because the pressure in the empty bladder measured 2.2 cm. At a pressure of 3 cm. the bladder held 2.2 c.c. of water. Stimulation caused 0.7 c.c. of fluid to leave the bladder, and then effected a 0.7 c.c. increase above the original volume. After relaxation became effective, fluid entered the bladder slowly, and about a minute after stimulation ceased the bladder regained its original volume. The amount of water leaving the bladder on initial stimulation remained less than 1 c.c. and decreased in amount as the viscus reached its capacity. The volume of fluid entering the bladder with relaxation increased, became maximal when the organ was half full and then, as it reached the limit of its capacity, decreased in amount. At a 7 cm. pressure and a 21.6 c.c. volume, the amount of fluid added to the volume by stimulation of the sympathetics was 4 c.c.

The greater relaxation of pressure in Graph A was obtained when the bladder was approximating the limits of its capacity. The second chart, B, makes it clear on the other hand that this marked change in pressure does not mean that the greatest increase in volume can be induced on sympathetic stimulation at this time. The increase in volume is greatest when the bladder is moderately filled. Then a slight decrease in pressure allows a large quantity of fluid to enter the bladder. When the bladder is full a marked change in pressure is related to only a small change in volume. Evidence that sympathetic stimulation effects a more marked relaxation when the parasympathetic fibres have been thrown out of function will be forthcoming later on in this paper.

THE EFFECT OF REMOVAL OF THE SYMPATHETIC INNERVATION OF THE BLADDER.

No one, as far as the authors are aware, has studied experimentally the effects upon bladder pressure and volume resulting from section of

the sympathetic nerve supply. It is true that Learmonth states that a transient frequency follows the operation in man, but in his clinical cases he gives no clear explanation of the functional improvement following section of the sympathetics. The present experiments show that it would not be possible to evaluate and analyse accurately the results of sympathectomy unless pre-operative studies of normal bladder function are made.

In the present experiments the sympathetics were approached retroperitoneally through a left lateral incision. In the earlier studies,

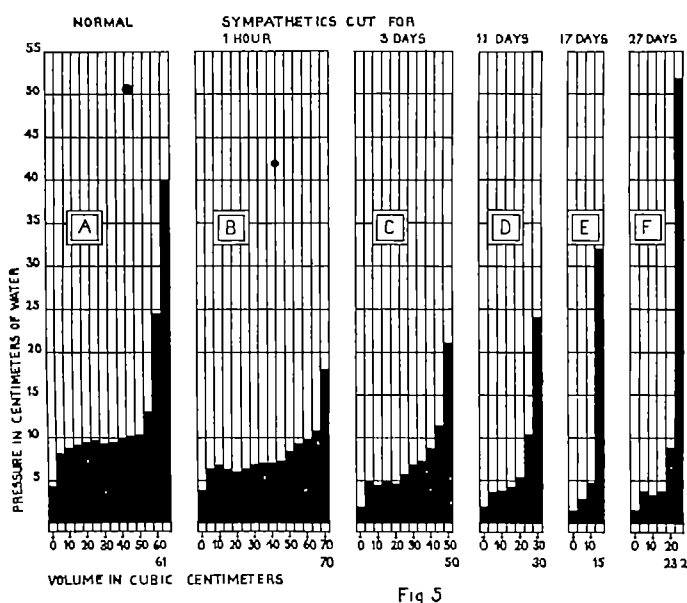


FIG. 5.—This diagram shows the pressure and reflex volume in the bladder just before and after section of the hypogastric nerves and the decrease in volume following the operation. Note the effect of the section upon the pressure at which the sphincter relaxed.

the hypogastric nerves were isolated and removed, but later on, to avoid the possible regeneration of these fibres, both lumbar sympathetic chains were exposed and taken out along with the ganglia.

The striking results of these experiments are perhaps best presented by discussion of the graphs. The effect of section of the sympathetics upon the pressure at which the sphincters relaxed was not observed in all of the cases; an example in which the sphincter changes are apparent was chosen for the first demonstration. Graph A in fig. 5 shows the pressures in the normal bladder after the addition of fluid increments.

This bladder emptied reflexly at a fluid pressure of 39.8 cm. and a fluid volume of 61 c.c. The bladder pressure remained below 10 cm. of water until the viscus was almost completely filled. After the sympathetics had been removed and the wound closed, a second determination showed the bladder to have a capacity of 70 c.c. instead of the former 61 c.c. This slight increase in bladder capacity, which is seen immediately after section of the sympathetics, is probably dependent on the long period of the anæsthesia and the shock of the operation. The sphincters which relaxed in the normal cat at a pressure of 39.8 cm. now relaxed at 18 cm.

The next three graphs (C, D and E of fig. 5) show, during the first three weeks after the operation, a progressive decrease in the volume required for reflex micturition and a progressive increase in the pressure at which the sphincter relaxed. Thus, the reflex capacity was 50 c.c. on the third day, 30 c.c. on the eleventh day, and only 15 c.c. on the seventeenth day. The pressure at which the sphincter relaxed rose to 21 cm. on the third day, 24 cm. on the eleventh day, and 32 cm. on the seventeenth day. The effect upon the pressure at which the sphincter relaxed was observed immediately after the operation, if at all, and was only transient. The change in reflex capacity of the bladder was constant and developed slowly over a period of days or weeks. When the sympathetics had been removed, the bladder held increments of fluid at lower pressures than it did in the intact preparation. The initial reading with the bladder empty was lower, 2 cm. rather than 4.3 cm. in the normal cat. Moreover, the bladder was less irritable to stretch stimuli and less spontaneous waves were seen. As the bladder was distended with increments of volume, the pressure rises increased by a series of steps, and there was less tendency for an accommodation of varying volumes at the same pressure than was found in the normal bladder. With increased volume the successive increases in pressure are of course accentuated by the fact that the bladder has become smaller in size. The pressure rises resemble those seen in the dead relaxed bladder shown in Graph B of fig. 3.

At the end of twenty-seven days, the bladder pressure at the time of sphincter relaxation was greater than in the normal preparation, 52 cm. as opposed to 39.8 cm. The reflex capacity was greater than ten days before, 23.2 c.c. instead of 15 c.c. Further studies, not shown in the figure, demonstrated a further progressive increase in the volume required for reflex micturition, so that on the forty-eighth day post-operatively the bladder held 45 c.c. at a pressure of 48 cm. of water.

It held approximately two-thirds of the volume of the normal viscus. In this animal the hypogastrics had been cut, and it seemed not unlikely that the sympathetic fibres had regenerated. Therefore on the forty-eighth day after the first operation the abdominal sympathetic trunks were exposed and removed bilaterally. Again the pressure at which the sphincter relaxed decreased at once and the bladder became progressively smaller. On the tenth day after the second operation the bladder emptied at 22.5 c.c. with a water pressure of 30 cm. Soon afterward the cat died of a respiratory infection, ending the experiment prematurely.

The other studies which will be reported now avoided this possibility of sympathetic regeneration, at least to a much greater degree, because the sympathetic chains were removed either unilaterally or bilaterally in one piece from the lower surface of the diaphragm to the sacrum.

The bladder capacity required for reflex micturition under anaesthesia varied enormously from one animal to another, although remarkably constant for a single normal animal. The values range from 12 to 260 c.c., and although this variation depended to some extent upon the age and size of the cat, by no means were these the most important factors. It had also a relationship to animal behaviour and activity; very irritable and excitable animals in general had small bladders. It perhaps also had to do with previous habit training. Subsequently it will be shown that large bladders are more markedly influenced by section of the sympathetic nerve supply than are medium-sized or small bladders.

In certain of the experiments, the abdominal sympathetic chain was removed unilaterally and the resulting bladder capacity determined; later, when the capacity had remained relatively constant for weeks, the second sympathetic chain was cut. A description of typical experiments will indicate the results obtained.

Two of the preparations had bladders of unusual capacity, 235 c.c. and 230 c.c. In both cases the volume dropped to less than half the original amount five days after the operation, and in fifteen days to less than one-fourth of the original amount. In one the reflex volume continued to decrease in size to 26 c.c. on the thirtieth day post-operatively. During the fourth week the capacity of one of the bladders took an upward swing and remained about 80 c.c. On the thirtieth day following the first operation in one case and on the thirty-fifth day in the other, the second sympathetic chain was removed. The smaller bladder then maintained the reflex capacity of 30 c.c., while the reflex volume of the

other decreased to 47 c.c., its smallest volume after the first operation. These animals were followed for seventy days after the first operation. At the end of this time one bladder had a reflex volume of 28 c.c., the other of 46 c.c.

Another experiment tested bladder capacity after unilateral and then bilateral sympathectomy in a cat which originally had a bladder of medium reflex volume, 89.5 c.c. At the end of the third week after operation, the bladder reached its smallest reflex size of 20 c.c. Then there occurred a slow increase in volume which led to a bladder capacity of 48 c.c. during the sixth week. With the bladder capacity fairly constant, the second abdominal sympathetic chain was removed. The capacity fell again to 20 c.c., the lowest reading previously recorded, but thereafter became elevated and remained constant at the same level at which it became stable following the first operation.

It is clear that the decrease in bladder capacity is as great after unilateral sympathectomy as it is when both sympathetic chains are removed. For normal sympathetic inhibition then, it is essential that the bilateral innervation be intact.

It is interesting to compare the effect of bilateral sympathectomy upon the bladder capacity of two animals possessing a marked difference in normal reflex volume. The bladder of one had an initial capacity of 120 c.c.; of the other 30 c.c. On the fourth day after the operation, the reflex capacity of the large bladder decreased to 30 c.c., and then following a fluctuation of increased volume reached a 21-c.c. capacity on the forty-sixth day post-operatively. The bladder with the original 30 c.c. capacity was reduced to 5 c.c. on the seventeenth day, but increased in size slowly to a peak of 23 c.c. on the thirty-fifth day. The volume then slowly decreased again. The final readings were made on the seventieth day after the operation. At that time the capacities of the two bladders were practically equal, 16 and 22 c.c.

After removal of the sympathetic innervation, the greatest diminution in volume is obtained in the bladder, which requires the largest normal volume for reflex micturition. A small bladder may show a considerable decrease in size after sympathectomy, but later its volume tends to approach although not to reach the normal. After sympathectomy, the bladders of the experimental preparations tend to approximate a mean capacity of from 20 to 50 c.c.

In two animals of our series the results deviated from those previously described. After unilateral sympathectomy, the reflex capacity in one of the cats became greater than normal, but after the removal of

the second sympathetic chain the volume of this bladder was reduced to less than the normal reflex capacity. The second cat showed a decrease in reflex capacity after unilateral sympathectomy, a decrease, however, that was not maintained, the volume increasing eventually to normal. Although the decrease was not striking, removal of the second sympathetic chain lowered the volume below the normal amount. These results indicate the variations in sympathetic control of the bladder in different preparations.

The decrease in size of the bladder after sympathectomy could be demonstrated by abdominal palpation. The cat has a very long urethra and the bladder normally lies high in the abdomen. After sympathectomy the bladder is pulled down into the pelvis and remains in this position almost constantly.

THE EFFECT OF SECTION OF THE PARASYMPATHETIC NERVES TO THE BLADDER.

Two types of operations were used to cut the parasympathetic fibres. The spinal canal was opened and the sacral roots cut near their origin from the cord or the sacral cord was removed if a bilateral effect was desired. In the other method, the second, third and fourth sacral roots were isolated in the pelvis. A bilateral operation of the second type required two incisions; the sciatic nerve was followed into the pelvis, the roots isolated by careful dissection and cut. The results of these two procedures were similar and no further distinction will be made. The approach into the spinal canal is undoubtedly the easier. Both of these sections paralyse the internal pudendal nerve.

The results of unilateral section are recorded in fig. 6; reflex micturition in the normal preparation under ether is demonstrated in Graph A. The cat's bladder emptied reflexly on a volume of 48 c.c. at a pressure of 44 cm. The sacral nerves were then cut upon one side. In three days a second determination was made and the bladder was found to be larger than formerly, for it held 70 c.c. and relaxed at 38.2 cm. A period of twenty-one days from the time of operation was then allowed to elapse before a second reading was made. At that time the reflex capacity had decreased to less than its original size, so the bladder emptied on a volume of 33 c.c., and at a pressure of 42 cm. These changes in bladder capacity are characteristic of parasympathetic lesions whether the injury is unilateral or bilateral. For a few days after the operation the bladder volume is increased, but later it shrinks to something less than its original size.

After unilateral injury of the parasympathetic fibres, the cats failed to show any evidence of incontinence and apparently emptied the bladder quite normally. On the other hand the bladder wall became thickened as evidenced by palpation and by post-mortem examination. Although this change involved both sides of the bladder there was an evident difference on the two sides, the thickening being definitely greater on the paralysed side.

For a comparison of the effect of unilateral and bilateral parasympathetic lesions, the sacral cord was then removed in the same preparation: the results are shown in fig. 6 (Graphs D and E). When

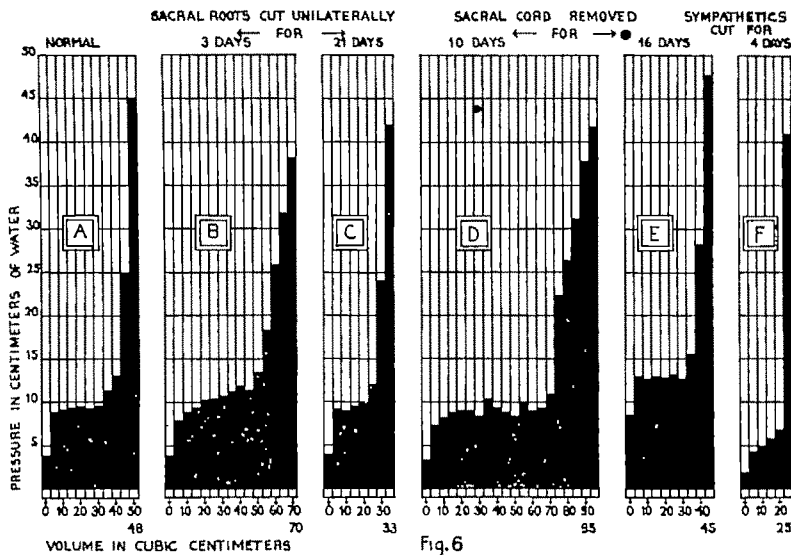


Fig. 6

FIG. 6.—This figure shows the effect upon bladder volume and pressure of unilateral and then bilateral section of the parasympathetic fibres. Afterwards the abdominal sympathetic chains were removed and the result is shown in diagram F.

the first reading was made, ten days after removal of the sacral cord, the bladder held a large quantity of fluid, 95 c.c. as compared with 48 c.c. in the intact cat (Graphs A and D). The type of diagram used here affords an inadequate picture of the bladder behaviour at this time. The muscle was irritable and responded with very marked contractions to the stretch caused by the addition of fluid. These contractions were largest early in the filling of the viscus and decreased in size as the bladder neared the limits of its capacity. The waves of contraction increased the pressure in the bladder as much as 14 cm. The intra-vesical pressure remained high after the introduction of fluid, and it was

necessary to wait some time to obtain the lowest possible readings. Moreover, the muscle was sensitive to ether and an increase in the depth of the anæsthesia caused a pressure rise. When the bladder was filled it did not empty, instead only a few drops of fluid escaped from the urethra. The viscus at this time showed the late stages of paralysis following bilateral lesion of the parasympathetics. Although small quantities of fluid escaped from time to time when the bladder was full, the contraction of the wall was not sufficient to expel the fluid. At frequent intervals the bladder had to be emptied manually.

After the operation, the function of the lower bowel was abnormal; the rectal sphincter was widely dilated and the mucosa everted. Marked constipation persisted and presented one of the greatest obstacles in caring for and preserving the animals.

A second determination of bladder capacity was made sixteen days after removal of the sacral cord when automatic micturition had become established (Graph E, fig. 6). During the six days following the last reading, a great decrease in bladder volume had occurred. After the development of automatic micturition, the bladder capacity usually becomes slightly less than that of the normal cat; the bladder now emptied on 47.5 c.c. at a pressure of 48 cm. The bladder muscle was now even more irritable than at the time of the previous reading. Increase in the depth of the anæsthesia caused contractions of the muscle, and the introduction of fluid increments elicited waves of contraction in response to the stretch of the muscle. After the introduction of fluid the intravesical pressure was always high and the lowest obtainable readings exceeded those recorded at previous times upon the same bladder. The initial pressure with the bladder empty was 8.5 cm. of water.

The cats with the sacral parasympathetics removed were a great nursing care. After automatic micturition was developed they were always wet and the perineum was œdematous. Usually the bladder became infected shortly after catheterization was started, and this infection was difficult to control. In our experiments bladder infection was almost pathognomonic of parasympathetic injury, for it seldom occurred in the other animals. One of the principal technical difficulties arose from the stasis of the gastro-intestinal tract and the resulting anorexia.

Palpation of the bladder through the abdomen revealed a thickening of the wall. This change in the bladder musculature was marked, when the organ was examined post-mortem.

STIMULATION OF SYMPATHETICS OF A CAT WITH AUTOMATIC BLADDER AFTER PARASYMPATHECTOMY.

Stimulation of the abdominal sympathetic chains in a cat with an automatic bladder following parasympathectomy gave more striking results than stimulation in the intact animal. Inasmuch as any increase in the intake of ether caused a contraction of the detrusor muscle, the anæsthetic was administered through a tracheal tube by means of an artificial respiration apparatus, and every effort was made to keep the anæsthetic constant. In Graph A of fig. 7 the equal increments of

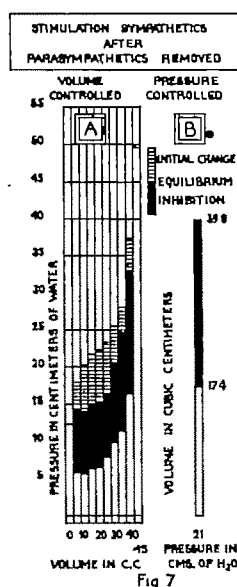


Fig. 7.—The effect of stimulation of the sympathetic chains upon pressure or volume in the bladder which is automatic after section of the parasympathetics is shown in this diagram. The black rectangles indicate the extent of the relaxation and the cross-hatched areas the initial rises in pressure.

volume are recorded on the ordinates and the pressure readings on the abscissæ. The upper edge of the black rectangle records the lowest pressure readings obtainable at a given volume before stimulation. The cross-hatched areas indicate the initial rise in pressure following stimulation and the black cylinders show the diminution of pressure which ensued. The pressure readings before stimulation are, of course, abnormally high; this is characteristic of the automatic bladder. Stimulation induced a quick rise of pressure which was followed by a slow fall to a pressure far below that recorded before stimulation.

The initial pressure with the bladder empty was 12.3 cm., and no change was noted on stimulation. With fluid in the bladder the rise and the ensuing relaxation could be demonstrated at each volume until the bladder was filled. The most marked rises occurred with the bladder volume of average capacity, and became less marked as the organ was approaching the limits of its capacity. No fluid ever escaped from the urethra when this rise in pressure occurred. As the bladder became filled the relaxation increased and was most pronounced with 40 c.c. of fluid in the cavity; it then lowered the pressure 16.7 cm. below the pre-stimulation level.

Due to the pronounced irritability of the bladder a chart could not be prepared to show the volume increase on sympathetic stimulation at all of the different levels of constant pressure, but the readings obtained at some of the pressure constants gave satisfactory information concerning the result. One of these readings is shown in Graph B of fig. 7. At the constant pressure of 21 cm. of water the bladder held 17.5 c.c. at equilibrium. Stimulation of the sympathetics effected no initial expulsion of fluid, but there at once occurred a rapid inflow of water to the bladder which continued until 22.4 c.c. had been added and the bladder volume increased to 39.8 c.c. On stimulation of the sympathetics the bladder volume was more than doubled.

This experiment demonstrates the power of the sympathetics over the automatic bladder. The initial rise undoubtedly represents a contraction of a portion of the bladder musculature; Elliott states that the sympathetics in the cat supply motor fibres to an area around the urethra. The contraction is more active than it is in the normal animal. The paralysed muscle is so irritable to stretch that it may augment the contraction of an isolated area. The diminution of pressure is also increased in these preparations. The pressure in the resting bladder is abnormally high, and the fall with relaxation lowers the pressure to a level that might be obtained on stimulation of the sympathetics in the normal cat. When the pressure is held constant, the volume may be doubled by sympathetic stimulation. Since it must not only expel fluid, but also cope with the inhibitory powers of the intact sympathetics, the bladder following parasympathectomy has to work against a double burden.

THE EFFECT OF SYMPATHECTOMY UPON THE AUTOMATIC BLADDER.

Testing the effect of sympathectomy upon the automatic bladder produced by previous parasympathectomy was the final aim of these

experiments. Considerable difficulty was encountered in maintaining the cats in good condition for the final operation. The findings are those which would be expected from the results already reported in this paper.

A re-examination of fig. 6 again emphasizes the effects of the previously discussed unilateral and bilateral parasympathectomy. Automatic micturition was established on a reflex capacity practically equal to that of the normal bladder. The abdominal sympathetic chains were removed and the next reading made four days later. The

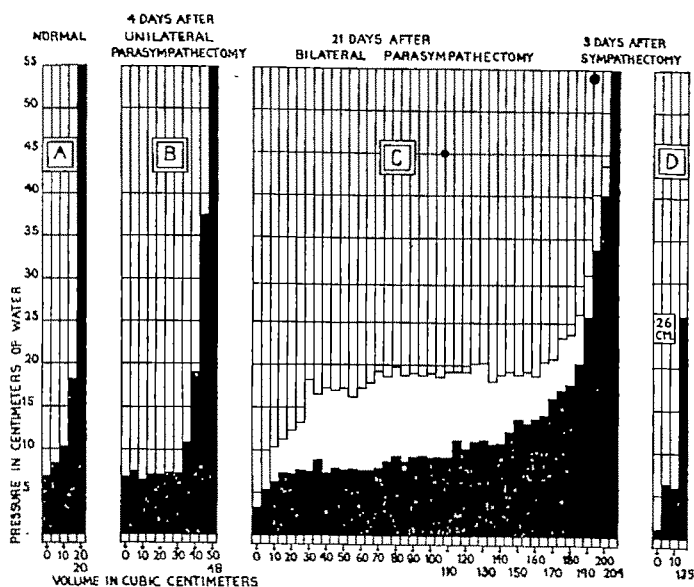


Fig 8

FIG. 8.—This figure shows the changes in bladder volume and pressure after unilateral and bilateral section of the parasympathetic fibres and subsequent removal of the abdominal sympathetic chains. The white area in diagram C indicates the extent of the waves of vesical contraction after fluid had been introduced and the observer was waiting for the lowest possible reading.

reflex capacity was reduced from 47.5 c.c. to 25 c.c. (Graph F, fig. 6). The sphincter of the automatic bladder relaxed at 47.5 cm. and after sympathectomy at 41 cm. of pressure. When the bladder was being filled the pressure readings were lower than previously and similar to those already described after sympathetic section. With the viscus empty there was an initial low pressure which thereafter rose by a series of steps with the increasing volume, and exhibited no faculty for holding the ranges of volume at the same pressure. This ability had been retained after the parasympathetics were cut.

Lumbar sympathectomy had its most marked effect upon the large bladder, and this moreover was true even when the large volume was absent in the normal animal, but was produced by nerve injury. This is demonstrated in fig. 8. The normal bladder of this cat had an extremely small volume for reflex micturition (Graph A): it emptied on 20 c.c. During the introduction of the increments of fluid, the pressure rose by a series of steps, the sympathetic nervous system normally exerting little control over this bladder. Four days after unilateral section of the parasympathetics, the reflex capacity had increased to 48 c.c. (Graph B). The parasympathetic fibres were then sectioned on the other side. Twenty days later the bladder was large and held 204 c.c. before fluid escaped from the urethra (Graph C). There was no infection of the viscus, but no decrease in reflex volume had occurred nor had reflex micturition developed. Within two weeks after the parasympathetics are cut, the bladder of the cat usually functions automatically.

The muscle was very irritable to stretch. The light area in Graph C of fig. 8 records the height of the contraction waves which occurred after the inflow of water had been stopped and the observer was waiting for the lowest pressure reading. The large volume of fluid was held at low pressures, and when the bladder was filled the pressure rose slowly by a series of steps, demonstrating an actual stretch of the elastic wall. As the bladder became distended, the spontaneous waves decreased in amplitude. At 204 c.c. fluid escaped from the urethra, but the bladder did not empty. Although the muscle of this bladder reacted forcefully to stretch, the viscus remained large and had not developed reflex micturition.

The abdominal sympathetic chains were then cut and the next reading taken three days later (Graph D). A dramatic change had occurred; palpation revealed that the bladder no longer lay in the abdomen, but in the pelvis. At this time its reflex capacity was 13.5 c.c., and the sphincter relaxed at 26 cm. The reflex volume was now less than in the normal cat. The bladder wall was still quite irritable to stretch, but not as much so as before the operation. Within three days the bladder capacity had decreased to one-fifteenth.

After sympathectomy there was a great improvement in the activity of the gastro-intestinal tract. Peristalsis of the large bowel became active again, and no longer was there an accumulation of faeces. The anal sphincter was less relaxed and eversion of the rectal mucosa less marked. Nevertheless, the reflex bladder in itself presented an obstacle to preserva-

tion of the cats, for they remained wet much of the time. They seldom could be kept in good condition for more than a few weeks.

Better chronic results were obtained in the few cases in which the internal pudendal nerves were spared, and the cats retained some control over micturition. Readings revealed that the bladder musculature reacted abnormally; the pressure readings were high, and the muscle was hyper-irritable to stretch. Following the operation the reflex volume was greatly increased and then became slightly less than normal. Under such conditions the reflex volume was decreased by sympathectomy and maintained its small size for months.

DISCUSSION.

The bladder differs from an elastic non-viable sphere in its ability to hold varying quantities of fluid at approximately the same pressure; this ability is a function of the smooth muscle within its walls and is dependent also upon the intact innervation of the muscle. As has been shown in this paper, the accommodation is affected seriously by the cutting of the sympathetic nerve supply. After the death of the animal the smooth muscle remains viable for hours, and during this period the ability to hold increasing amounts of fluid at the same pressure is much less marked than in the live preparation; with the passage of time great diminution in this capacity is noted.

MacWilliams (1902), Osborne (1909) and Kesson (1913) have written of the elasticity of cavities formed for the most part of smooth muscle. MacWilliams studied the arterial wall during relaxation and in the state of post-mortem contraction. Osborne considered the elasticity of balloons and hollow viscera, including the bladder, while Kesson made observations upon the bladder. Flexner, Clark and Weed (1932) investigated the elasticity of the dural sac. The physics of elasticity in tensile membranes and particularly those of the living organs of the body becomes a complicated subject, but a graph showing our own observations (fig. 3) illustrates phenomena which help in understanding the activity of the bladder wall. Although manufactured rubber balloons were also examined, their properties differ so markedly from those of the bladder that discussion of the results would be unprofitable.

The irritability of the bladder is increased through its sympathetic innervation. This is evidenced by the increase in pressure which immediately follows stimulation, and by the decrease in irritability on section of the fibres. Sympathetic stimuli inhibit the tone of the muscle, permitting it to hold more fluid as well as varying quantities of fluid at approximately the same pressure. After sympathectomy the reflex

volume decreases, and with the addition of increments of fluid the pressure rises by a series of steps. Moreover, the recorded pressures in the bladder are lower than normal and the emptying mechanism appears to be more efficient. There are two opposing forces acting on the bladder through the medium of sympathetic stimuli. One produces a contraction of smooth muscle fibres at the base of the bladder and a slight rise in pressure, the other an inhibition of the detrusor muscle.

We have so far refrained from discussing the sympathetics in their relation to the sphincters. Our own experiments give only slight information concerning sphincter activity and at most record the pressure within the bladder at the time fluid escapes from the urethra. Moreover, we agree with the opinion of Denny-Brown and Robertson that the sphincters have little individual activity separate from that of the vesical musculature; the activity of the sphincters is related inversely to the activity of the detrusor muscle. When the tone of the bladder muscle is high, the tone of the sphincters is low: the reverse is also true. If the bladder muscle contracts forcefully, the sphincters relax and micturition always begins as an active and sustained contraction of the bladder musculature. Voluntary delay of micturition is effected largely through an inhibition of the contraction of the detrusor muscle, although it is also possible to increase the contraction of the external sphincter voluntarily. Often after sympathectomy little change was observed in the pressure at which the sphincter relaxed. In most instances, if a determination was made immediately after removal of the sympathetics, a decrease was noticed in this pressure. After a period of several days the pressure returned to its former height or was even higher.

Recently some doubt has been raised as to the part played by the sympathetics in the voluntary inhibition of micturition in man. This function may of course be considered either an active inhibition through the sympathetics or a decrease of the normal activity of the parasympathetics. Denny-Brown and Robertson (1933 A) demonstrated in normal man active inhibition of the waves of bladder contraction by an effort of the will. In individuals with complete section of the parasympathetics, but with the sympathetics intact, they maintained that this cerebral control was lost (1933, B). They believe, therefore, that cerebral inhibition of micturition is effected through the agency of the parasympathetics. This, of course, is possible, but the work reported here reveals such a marked decrease in bladder volume for reflex micturition following sympathectomy that it seems rather evident that all the inhibition of bladder function is mediated through the sympathetics.

Whether this is actually true for voluntary control will be a problem for further study.

Learmonth reported that patients notice a transitory frequency after section of the sympathetics. The present experiments demonstrating a marked decrease in bladder capacity after sympathectomy make one conjecture concerning the subjective results in terms of frequency. Normal voluntary micturition usually is initiated before the bladder has reached the limits of its capacity, whereas reflex micturition under anaesthesia is effective only when the bladder is filled completely. It is probably rare in man that the bladder is ever completely filled. Under such conditions a great change in bladder capacity might be noticed during the period when the reflex volume was decreasing, and would no longer be observed when the bladder became fixed at a constant lower capacity. After sympathectomy the pressure rises more rapidly when the bladder is filled, and this may be appreciated as urgency.

The authors are able to give little specific information concerning the improvement in function of the automatic bladder after sympathectomy. It may be said that the extremely irritable muscle of the automatic bladder is inefficient, and that the energy is utilized in holding the volume at a constant high pressure. The decrease in irritability and in intravesical pressure after sympathectomy may increase its efficiency. When the emptying mechanism is weak, a small volume may be expelled more easily than a large one. The bladder remained at a decreased volume following sympathectomy. One thing is clear: a bladder of initial large size will show a great diminution in reflex volume after sympathectomy. This is true whether the large volume is normal or dependent upon a lesion of the parasympathetics.

The sympathetics are in no way essential to normal micturition. In certain mammals they have developed an inhibitory control over the detrusor muscle which enables the animal to increase the interval between micturitions by enlarging the bladder volume. This advantage becomes a liability if the parasympathetic innervation is damaged as the inhibitory power renders emptying more difficult. If the sympathetics are then cut to make expulsion of urine more efficient, care should be taken to plan an operation which would prevent the regeneration of the fibres.

SUMMARY.

Stimulation of the sympathetic fibres to the urinary bladder causes a quick rise of intravesical pressure followed by a slow fall to a point below the reading before stimulation. If the pressure is maintained at

a constant level and the sympathetics stimulated, a small amount of fluid first leaves the bladder and then a greater quantity enters the viscus, so that the bladder holds more than it did before the stimulation occurred. The results of stimulation are much more striking if the parasympathetics to the bladder have been sectioned a few days previous to the experiment.

After section of the sympathetics to the bladder, the viscus holds fluid at lower pressure than normally and loses the ability to hold varying quantities at approximately the same pressure. The muscle is less irritable, but the emptying reflex is somewhat more forceful than before. The quantity of fluid required for reflex micturition falls steadily during the first few days after sympathectomy. The decrease in volume after sympathectomy is greatest in bladders of large initial capacity.

After unilateral section of the parasympathetics, the function of the bladder musculature is impaired. When the parasympathetics are cut bilaterally, fluid is held at a pressure higher than that before operation and the muscle is extremely irritable. For the first few days after parasympathetic injury, the bladder has an increased capacity, but this falls somewhat lower than that of the normal when automatic micturition begins.

Removal of the sympathetic chains under these conditions of automatic micturition produces the same changes that have been recorded for this operation upon the normal animal. These are indications that the function of the automatic bladder is improved by section of the sympathetics.

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PLATE XII.



FIG. 1.—Myeloma showing an area of undifferentiated cells. (Case 1.)

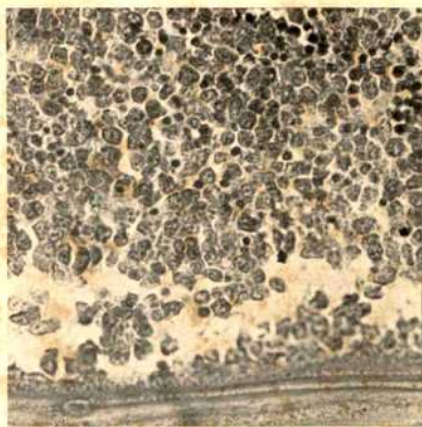


FIG. 2.—Myeloma. In this field the tumour cells resemble myelocytes. (Case 1.)

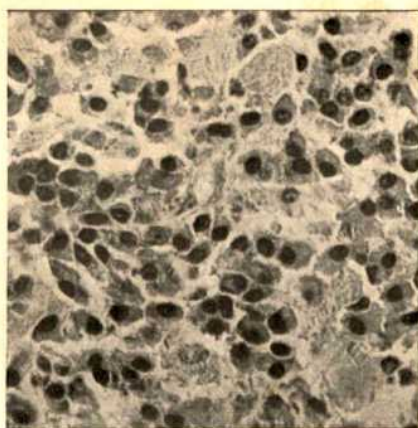


FIG. 3.—Plasma cell myeloma. (Case 2.)

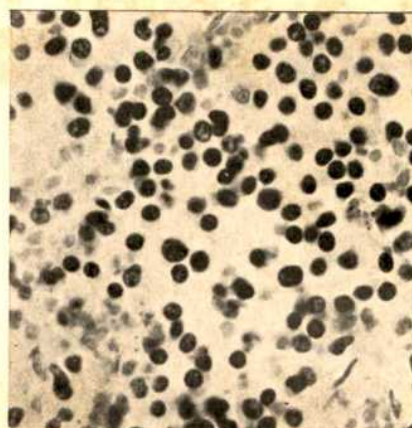


FIG. 4.—Plasma cell myeloma. (Case 4.)

THE GENERALIZED AND VERTEBRAL FORMS OF MYELOMA: THEIR CEREBRAL AND SPINAL COMPLICATIONS.¹

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MYELOMA may be regarded as a malignant tumour of bone-marrow arising either from a single-cell type, the plasma cell, or perhaps from a number of different bone-marrow elements. Depending upon the type cell—(1) plasmocytomas, (2) erythroblastomas, (3) myelocytomas, and (4) lymphocytomas have been differentiated in the myeloma group (Ewing [1]).

There is still a good deal of difference of opinion concerning the pathogenesis of these growths. Most pathologists regard either the plasma cells or the myeloblasts of the bone-marrow as the original cells of the growth. Others, including Christian [2], believe that the type cell is a transitional form, neither a plasma cell nor a myelocyte. In view of the almost constant bone resorption so characteristic of this tumour, the osteoblast has even been thought to be the type cell (Williams [3]). A very different conception of myeloma has been advocated by Witzleben [4], who regards it as a systemic disease of the blood-forming organs, closely allied to the leukemias, but aleukemic in nature, with predominant participation of the bone-marrow and the occasional involvement of other hematopoietic tissue. Lubarsch [5] believes that the myelomas belong to the group of hyperplastic, and not to the truly neoplastic diseases. An unusual case reported by Jackson, Parker and Bethea [6] is interesting in this connection. They describe a patient with a plasmocytoma of the tonsil removed eight years before generalized bone involvement could be detected. During the seven quiescent years "the process was spreading through the lymphoid system, as was proved by successive lymph node involvement, and eventually bone lesions characteristic of multiple myeloma made their appearance."

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The histology of the removed lymph nodes and of the bone tumours at autopsy was identical, i.e. plasma cell myeloma. These authors believe that the plasma cell tumour arose in the tonsil and spread through the lymphatic system, finally to enter the bone-marrow. They classify the plasma cell myeloma among the malignant lymphomata, rather than with the true bone-marrow tumours.

The disease is rare. Symmers and Vance [7] found only three cases in 4,000 successive autopsies at Bellevue Hospital, New York City. Four instances occurred in 9,000 consecutive autopsies at the Johns Hopkins Hospital, Baltimore.

The flat, short bones, viz., the ribs, sternum, scapulæ, skull and vertebræ, are especially involved. Soft grey or reddish grey masses start in the marrow, grow outward and replace the cortex of the bones. Secondary growths may appear in the liver, spleen, kidneys, lung and sex glands.

Myeloma occurs in the later period of life; 80 per cent. of Geschickter and Copeland's [8] series was between the ages of 40 and 70, with the greatest incidence at 55 years. Only five cases were found in people under 35, and of these two were not proven microscopically. It occurs twice as often in males as in females. In almost all cases there are multiple tumours. Pathological fracture of a rib or vertebra is a frequent late occurrence; in no other type of bone tumour does pathological fracture occur so frequently (62 per cent. of all cases). Bence-Jones bodies were found in the urine in 65 per cent. of Geschickter and Copeland's series, and in 80 per cent. of Magnus-Levy's [9] cases. The exact nature of these bodies, which precipitate between 50° and 60° C., only to disappear on further heating to 90° to 100° C., is not definitely known. They are not found exclusively in cases of myeloma, but have been reported in many diseases in which the bone-marrow is involved. A possible relationship between this peculiar albumosuria and the blood proteins is suggested by the hyperproteinæmia found in some cases by Magnus-Levy and Freund [10]. They point out that this is not due to Bence-Jones bodies, however, but possibly to some substance analogous to fibrin. Geschickter and Copeland [11] report a recent case in which the patient's plasma proteins were 12.3 per cent. as compared to an average normal of 6 to 7 per cent. In this connection, Paige [12] found an unusual amount of amyloid deposition in almost all the organs of her case. She thinks this significant and possibly related to the Bence-Jones bodies in the urine. Nephrosis, anæmia and a chronic low-grade fever are reported in many cases.

No definitely curative form of treatment for generalized myeloma is known. Craver and MacComb [13] report favourable results in five of a series of six cases by the use of Heublein's method of total body X-ray irradiation.

The prognosis in cases of myeloma is very grave. The average duration of life is two years, the longest duration of any proven case being five and one-half years.

Once the tumour has appeared in many bones, the diagnosis is easily made. The age-group (fifth and sixth decades), multiple involvement of the short flat bones of the trunk, pathological fracture of a rib, Bence-Jones bodies in urine, progressive anæmia, nephrosis and cachexia make a highly characteristic clinical picture.

As an example of the generalized form, the following recently observed case may be cited.

Case 1.—B.L. (B.I.H., No. 20450 and No. 45816), a girl, aged 15, was first admitted to the medical service of Beth Israel Hospital, New York (Dr. I. Held), on November 2, 1931.

The family history stated that a brother died at the age of 9 of diabetes mellitus. The past history was irrelevant.

Her present illness began in May, 1931, with a persistent pain in the left upper quadrant of the abdomen. Two months later she fell on her back which immediately became painful, a few hours later she vomited. Vomiting continued for one week and the pain in the back increased. For two weeks there was cessation of pain but she grew weaker rapidly and lost 20 lb. in weight. Seven weeks before admission she was removed to another hospital, her appendix and gall-bladder were removed. The surgeon felt nodules in the tail of the pancreas and enlarged lymph glands and spleen. She made a satisfactory post-operative recovery but continued to vomit once or twice a week. Two weeks before entry the pain in the back reappeared; at one time a sneeze produced such a severe exacerbation of pain that she fell to the floor in agony. Five days before admission constipation, headache and left-sided abdominal pain were complained of. Just before entrance she felt dizzy and vision became blurred. One hour later she suddenly lost consciousness and generalized convulsions set in which lasted four hours. She bit her tongue during the fit. After the movements ceased she sank into a deep stupor.

Examination showed a young girl in deep stupor, pale and dehydrated. Neurological examination revealed no abnormal signs, the eye-grounds were normal. No glandular or abdominal masses were found. There was a tachycardia of 140 and mild clubbing of the finger-tips; slight pretibial oedema was noted. After a number of hours the girl's consciousness began to return. There was definite abdominal tenderness. For the next weeks the patient complained of pains along the spine and in the lower ribs and long bones; a polydipsia was also noted. She gained 4 lb. in weight. For the first few days

the temperature ranged from 99° to 100·4° F.: the pulse from 100 to 148; the respirations from 22 to 26. Her blood-pressure was raised at first, the systolic ranging from 158 to 184 mm. H., the diastolic from 112 to 140: the blood-pressure reached normal levels after a few days. A tachycardia of 96 to 116, an increased respiratory rate of 24, and an irregular temperature range of 99 to 101 persisted week after week. Her weight was 106½ lb.

The spinal fluid examination revealed entirely normal findings.

X-ray report was as follows: "Diffusely scattered through the skull, pelvis, ribs and in the diaphyseal ends of the fibulæ, the humerus, radius, in the acromion process of the scapula, and the acromial ends of the clavicles are numerous, small, circular, sharply-defined areas of osteolysis which appear to be medullary in origin and to involve the flat bones more than the long bones. The lesion in the long bones is located for the most part in the cancellous ends with the exception* of the humerus where several foci are present in the mid-shaft on both sides but probably in the cancellated tissue. There is no expansion of bone, no periosteal reaction and no bowing or bending of the bones. The lesions show a tendency to confluence." Examination of the gastrointestinal tract showed no abnormality.

Electrocardiographic study showed a sinus tachycardia.

Examination of the blood: In the first two weeks of her hospital stay the red blood-counts ranged from 3,300,000 to 3,510,000 with hæmoglobin estimations of 56 to 67 per cent.; the white blood-counts ranged from 7,100 to 19,200 with an average of 13,000; the differential count averaged: polynuclears 70 per cent.; mononuclears 30 per cent. In the latter weeks the red cells numbered 2,850,000 to 3,850,000, with hæmoglobin at 51 per cent. The previous leucocytosis gave way to a leucopenia ranging from 4,800 to 7,000 cells with polynuclears 42 per cent.; mononuclears 58 per cent. Four sedimentation rates averaged 63 per cent. Blood chemistry CO₂: 74·5 per cent.; glucose averaged 100 mgm. on three tests; sugar tolerance curves were normal. The non-protein nitrogen averaged 44 mgm. on three tests; calcium 9·2 to 9·8 mgm.; phosphates 3·2 mgm.

Nine examinations of urine made between November 2 and November 6 showed faint traces of albumin on three occasions. Bence-Jones bodies were sought on three occasions in vain.

The basal metabolism was minus 7 per cent.

Because of the history of a "nodular pancreas" felt at operation and the convulsions, adenoma of the pancreas was believed to be present, but blood sugar studies failed to substantiate this diagnosis. Moreover, the X-ray findings pointed to diffuse bony disease. The diagnosis on discharge, December 8, 1931, was generalized xanthomatosis.

She was readmitted to the hospital on January 10, 1932. Generalized malaise, headache, polydipsia and vomiting had continued. On January 6, 1932, she complained of painful gums; two days later she fainted and was stuporous for a number of hours; then she became overactive, danced about and sang while in bed. Convulsive seizures lasting one and a half hours

occurred on the day before admission. At this time she was pale, greatly excited and incoherent (post-epileptic state); this agitation alternated with periods of semi-stupor. A small exostosis was found in the right frontal region. The temperature varied from 99° to 100° F., the pulse-rate from 106 to 132 and the respirations varied from 18 to 24. The blood-pressure on admission was S.168/D.130; later S.130/D.90. Her weight was 97½ lb. Neurological examination was again negative. Glucose injections were of no benefit. In two days she became coherent, quiet and comfortable. Within ten days dizziness, headache and vomiting reappeared. During this period her blood-pressure was raised S.156/D.116. X-ray therapy was given to the skull; despite thirteen treatments there was no regression of the pathological process.

Early in February, 1932, the ribs felt nodular and a lower thoracic kyphosis appeared. In March, 1932, the audiogram showed slight bilateral diminution in hearing, more marked on the right. In the next few months she went rapidly downhill. Pains in the head, teeth, ribs and spine were complained of. The lower thoracic kyphosis became more marked. She vomited occasionally. A sacral bed-sore appeared. In March the spleen was felt. The tachycardia and moderate hypertension continued. Oedema began late in June, especially over the ankles, it spread to include the face and became generalized. She died on July 24, 1932, in a state of advanced cachexia.

During the period of her second stay in the hospital the spinal fluid showed an increased pressure of 205 mm. and increased protein to 130 mgm.

X-ray examination: "There has been a considerable increase in the number and size of the areas of osteolysis in the various bones previously mentioned. In the ribs are multiple lesions with expansion of their cartilaginous ends. The vertebrae show diffuse involvement. The upper ends of both humeri and the ends of the clavicles contain multiple foci which have a tendency to coalesce. There is an area of osteoclasia in the region of a lower molar tooth in the right lower jaw. There are no changes in the left half of the mandible. There is irregular atrophy with lacunar destruction of the posterior portion of the right os calcis; there are similar lesions at the end of the epiphysis of the right tibia in juxtaposition to the fused epiphyseal line. There is a slight perforation of the cortex at the posterior surface of the lower end of the tibia. The proximal end of the metatarsal bone of the big toe shows a linear area of irregular atrophy. There is a similar distribution of atrophy in the distal ends of the second to the fifth metatarsal bones and in the proximal end of the proximal phalanx of the big toe."

Six blood-counts revealed a progressive anaemia, the counts ranging from 3,300,000 to 1,910,000; anisocytosis, poikilocytosis, polychromatophilia and toxic degeneration of neutrophils were noted. The haemoglobin sank from 49 to 33 per cent. The reticulocyte count was 1.2 per cent. A white cell count of 6,400 with an average count of 71 per cent. polymorphonuclears and 29 per cent. mononuclears was found. Coagulation time was four minutes on one and three minutes on another occasion. The blood phosphatase was increased.

Estimation of the blood proteins gave the following figures.—

		62.82	114.32	185.82	286.82	67.82
Total protein	..	5.50	4.68	4.28	4.20	4.25
Albumin		2.81	2.95	1.56	1.75	1.98
Globulin		2.69	1.73	2.72	2.45	2.32
Albumin-globulin ratio		1.0	1.7	0.57	0.71	0.88

Twenty-one urine examinations showed traces of albumin; a number showed hyaline and granular casts; the specific gravity remained low (1005 to 1012). Bence-Jones bodies were again sought for in vain on different occasions. On January 28, 1932, the xylose test showed definite impairment of renal function, the maximal concentration being 0.65 per cent. (normal 2.5 per cent). On February 4 doubly refractive bodies were found in the urine.

A biopsy from a rib was made. The consistency of the rib was fairly normal. Its cut surfaces had some brown irregular areas. Microscopically the picture was that of a myeloma showing a rather indifferent small type of cell, the average size being 5 to 6 micra (Plate XII, fig. 1). The cytoplasm was indistinct, the nuclei were dense and without regular structure. No reticulum was seen. The outlines between the tumour and the surrounding bone marrow were indistinct, there were very few places only where a fine layer of connective tissue separated the myeloma from normal bone marrow. There were many thin-walled capillaries. An occasional area was occupied by more highly differentiated cells resembling myelocytes (fig. 2).

There was an incomplete autopsy. Some material was available from the spleen, kidney, pancreas, liver, and intestine. The kidney and liver contained more or less well outlined areas corresponding in structure to the myeloma described above. In addition many lime deposits were seen in the kidneys; these were attributed to widespread destruction of bone throughout the body. The pancreas revealed a most surprising picture. Grossly it appeared light yellow and unusually firm. Microscopical sections consisted mainly of dense connective tissue and contained only a small amount of pancreatic parenchyma, the condition of which could not be judged on account of post-mortem change. This, unfortunately, applied to the islands as well. Many of the pancreatic ducts were wide and contained homogeneous, partly broken-up masses. These did not consist of lime since they could be dissolved in inorganic acids and did not take the hæmatoxylin stain. One of the concretions was examined chemically for cholesterol but none was found. Only a small amount of inflammatory infiltration was seen in the pancreas.

The final pathological diagnosis was Multiple myeloma, myelomatous infiltration and lime deposits in the kidneys, myelomatous infiltration and severe fatty changes in the liver, severe atrophy and fibrosis of pancreas with concretions in the pancreatic ducts. (Dr. A. Plaut.)

Comment.—The unusual features of this case were the youth of the patient, the recurrent convulsions and the polydipsia. Among the laboratory findings, the marked involvement of the skull was of especial interest; in the post-mortem examination, the myelomatosis, the lime

deposits in the kidney and the atrophy and fibrosis of the pancreas with concretions of the ducts. The convulsions were readily attributed to the cerebral effects of the countless bony tumours in the skull. The polydipsia was regarded as part of a diabetes insipidus, due to bony invasion of the basilar parts of the skull with secondary effects on the pituitary gland or on the structures of the floor of the third ventricle. Diabetes insipidus has been described by Aronsohn [14] in a case of multiple myeloma due to such basilar involvement. This author discussed the cause of these secondary effects—whether induced by toxins, produced by pressure of the growth or by impairment of vascular supply. Direct pressure did not seem to play as important a part as in the vertebral type to be next described.

Neurological signs are found in 40 per cent. of cases of myeloma. As will be seen, paraplegia due to compression of the spinal cord is not uncommon. Signs of medullary disease, such as glossoplegia, dysphagia and alteration of voice due to paralysis of laryngeal muscles have been noted. Diplopia, Horner's syndrome, evidence of spinal root involvement and herpes have also been reported (Geschickter and Copeland [8]).

Since its original description, myeloma has always been regarded as a tumour of multiple incidence, hence the term "multiple myeloma." Ewing [1] does not even refer to their isolated occurrence. In a most exhaustive study of 425 cases reported in the literature, Geschickter and Copeland [8] conclude that "exceptions are so rare that the statement that myeloma is always multiple and always involves the trunk, is practically vindicated." Magnus-Levy [9] likewise is not convinced that any of the reported rare examples of solitary myeloma were truly proven. He points out that most of the cases were not autopsied, not followed long enough after the original diagnosis was made, nor thoroughly studied, especially by X-rays.

In a thorough search of the literature only three undoubtedly proven cases are found. These are: The rapidly fatal case of Cabot [15]—a man of 32 with a myeloma of the fourth thoracic vertebra; the lesion was found to be limited to this site at autopsy. The case of Geschickter [16]—a man of 45 with a plasma cell myeloma of the femur, proven by biopsy; X-rays of all other bones were negative and no Bence-Jones bodies were found. The case of Harding and Kimball [17], the myeloma being found in the femur of a man of 65; autopsy revealed only the one lesion.

Many of these "solitary" myelomas begin in a vertebral body and

announce their presence by signs of compression of the cord. Recent reports by Wakely [18], Jacox and Kahn [19], and Klemme [20], and our own experiences show that this vertebral form of the disease is not so rare. While the separation of this group from the pathological viewpoint may be an artificial one, it would seem justifiable on clinical grounds because for a considerable period of time the growth is confined to the vertebral and extradural tissues. Moreover, the patient may die before the growths become widespread. In this variety the typical picture presented is that of a man or woman in the fifth or sixth decade who rapidly develops the signs of a transverse spinal lesion with manometric block. The thoracic cord is usually the site of the cord compression; there is focal spinal tenderness. X-ray of the spine may be negative or show destruction of the body of the vertebra. No primary focus of malignancy can be demonstrated elsewhere. Laminectomy reveals a grey or reddish grey extradural mass either pushing the cord backward or encircling it. The growth can be traced frequently to the diseased vertebral body. Removal of the extradural mass decompresses the cord and great improvement follows the operation. Our third patient was relieved for two years before recurrence and pathological fracture occurred; the second patient, bedridden with a paraplegia, was enabled to get up and walk about. He is now transacting his daily business, nine months after operation. Jacox and Kahn [19] describe beneficial results from laminectomy in two cases and relief of root pains by the subsequent use of X-ray therapy. Klemme [20] also reports favourable results after laminectomy in four of his five cases. However, the ultimate outlook is very grave; a pathological fracture is the constant menace, together with the reappearance of the disease in other bones, leading to the signs noted under the generalized form of the disease, and finally death.

As examples of the vertebral form of myeloma, the following three cases are cited.

Case 2.—H. McC. (B.H. Neur. No. 679), a man aged 48, a mechanic by occupation, was admitted to the neurological service of Bellevue Hospital, on June 29, 1933.

The family and past history were irrelevant. He was a heavy drinker of alcohol for many years.

His present illness had a gradual onset, nine months before admission, with localized pains in the front of his right chest; these later radiated to the interscapular region posteriorly. The pains were aggravated by deep inspiration, sneezing or coughing, and became more severe; very recently they appeared bilaterally. For about two weeks before admission he also noticed

weakness and unsteadiness in his lower extremities, especially when he descended the stairs. His legs often felt numb as if "they were asleep," at other times as if he were walking "on something soft." There were no bladder symptoms nor any pains or weakness in his upper extremities. He lost about 10 lb. in weight since the onset of his illness.

Examination revealed a poorly nourished middle-aged man, not acutely ill. He was co-operative and of average intelligence. A bilateral hydrocele and a slightly enlarged prostate of regular normal consistency were noted. The spinous processes of the third and fourth thoracic vertebrae were slightly prominent and tender. The blood-pressure was S.120/D.80.

Neurological examination: The cranial nerves were normal. The gait was somewhat spastic. There was a marked weakness of both lower extremities, the right being weaker than the left. There was no atrophy, fibrillation or ataxia. Sensory examination revealed a loss of pain, light touch, and temperature sense below the fourth thoracic dermatome on the right and the seventh thoracic on the left; the peri-anal region was included in this impairment. Position sense was normal in the toes; vibration sense was moderately diminished up to the ankles. The deep reflexes were normal in the upper extremities. Both knee-jerks were overactive. An unsustained bilateral ankle clonus and a bilateral Babinski toe sign were found. The abdominal and cremasteric reflexes were absent.

Immediately after lumbar puncture increased weakness of the lower extremities with complete retention of urine developed. He became bed-ridden. The sensory level at thoracic-4 was accentuated with more marked hypalgesia below this level.

Spinal fluid examination disclosed a xanthochromic fluid under a pressure of 80 mm.; complete manometric block to jugular compression was present, but after cisternal puncture normal fluctuations to compression were found. The spinal fluid showed two cells with a total protein of 300 mgm.; the Wassermann reaction was negative.

X-ray of the spine showed destruction of the body of the fourth dorsal vertebra with some lateral buckling; no evidence of new bone formation was seen. X-rays of all other long bones, including chest, sternum and skull, were negative.

Examination of blood: hæmoglobin 75 per cent.; red blood cells 3,900,000; white blood cells 11,000; polynuclears 70 per cent.; lymphocytes 26 per cent.; transitionals 2 per cent.; eosinophiles 2 per cent. Non-protein nitrogen 30 mgm.; blood sugar 77 mgm. per 100 c.c. of blood.

The analysis of the urine was negative, though repeatedly examined for Bence-Jones bodies, but none were found.

On July 6, 1933, Dr. D. Klenke performed a laminectomy (second, third and fourth thoracic segments). A large tumour mass was found invading the body of the fourth thoracic vertebra. The tumour also involved the posterior right half of the arch. The dural sac was bent backward by the tumour at the level of the fourth thoracic vertebra. The growth was removed extra-

durally, completely relieving the angulation and restoring normal pulsations in the cord. It was felt that the tumour had arisen from the bone itself and could, therefore, not be completely removed, although practically all of the intra-spinal portion was excised. The tissue proved to be a typical plasma cell myeloma (Dr. Douglas Symmers) (fig. 3).

The post-operative course was uneventful. There was gradual improvement and return of strength in the lower extremities and complete relief of pain. Deep X-ray therapy was immediately begun. At the time of discharge from the hospital on December 27, 1933, he was able to walk up and down the wards without support, except for a brace applied to his back. By the end of January, 1934, he had finished two courses of radiation therapy of ten treatments each. He was walking well except for some slight spasticity. There were no bladder disturbances. There was no further loss of weight. He still showed overactive knee and ankle jerks. His plantar reflexes were equivocal. A slight abdominal flicker was obtained on the right, none on the left. The sensory changes had completely disappeared. He was examined again on April 13, 1934. His gait was a little spastic and insecure; no Romberg sign was elicited. The knee and ankle jerks were still over-active. There was a left Babinski toe sign. The abdominal reflexes were absent. A level was found at thoracic 6, below which there was very slight hypæsthesia and hypalgesia; temperature, position and joint and vibratory senses were intact. He noted an occasional trifling urinary incontinence.

X-rays of all other long bones, chest, sternum, pelvis and skull continued to be negative.

Case 3.—M. M. (B. H. Neur. No. J 182), a mulatto housewife, aged 48, was first admitted to the neurological service of Bellevue Hospital on March 8, 1928.

The family and past history were irrelevant.

Her present illness began two months before entry with gradual weakness in the lower extremities. The weakness was first noticed in the left knee; later the left ankle would turn in as she walked, causing her to trip. The disability became worse, and one week before admission power in the right leg also became affected in a similar way. She also complained of numbness and coldness in the legs. There were frequent attacks of severe pain beginning in the lumbar region and radiating down both thighs to the calves. There were no bladder symptoms.

Examination revealed a middle-aged mulatto woman in a good state of nutrition. There was a moderate amount of tenderness over the second thoracic vertebra. The blood-pressure was S. 178/D. 110.

Neurological examination.—The cranial nerves were normal. There was great weakness of both legs, more marked on the left. The knee-jerks were overactive, the left being greater than the right; a left patellar clonus was elicited. Both ankle-jerks were absent. There was a definite Babinski sign on the right; the left plantar response was equivocal. The abdominal reflexes were absent. Motor power and all the reflexes in the upper extremities were

normal. There was a defect to all forms of sensation, except position sense, which was intact up to the fifth thoracic dermatome; the peri-anal region was also involved.

Spinal fluid examination disclosed a clear, colourless fluid with sixteen cells per c.mm.; globulin was much increased, Wassermann negative, colloidal gold curve 4438221000. The pressure was 145 mm.; there was a complete block to jugular compression.

X-rays of the spine showed an erosion of the third, fourth and fifth thoracic vertebræ; the body of the fifth was completely compressed. The inter-vertebral spaces between the third, fourth, fifth and sixth thoracic vertebræ were entirely obliterated. X-rays of the skull, the chest, ribs and all the long bones were negative.

The blood Wassermann was negative. Examination of the blood: hemoglobin 60 per cent., with 3,500,000 red blood cells; 7,800*white blood cells; 66 per cent. polynuclears; 30 per cent. lymphocytes and 4 per cent. basophiles.

Analysis of the urine was negative; repeated examinations of the urine for Bence-Jones bodies were negative.

Operation was performed on March 28, 1928 (Dr. Alfred S. Taylor). Laminectomy over the third, fourth, fifth and sixth thoracic vertebræ revealed thin, diseased bone infiltrated by an extradural tumour which compressed the spinal cord and encircled the dura. There was a fixed portion anteriorly and to the right. Most of the growth was removed in fragments. The tumour involved the body of the fifth thoracic vertebra, so that complete removal was impossible. At the end of the operation the dura pulsated normally with respiration.

The post-operative course was one of gradual improvement. Deep X-ray therapy was begun. In a few weeks the patient was able to get up out of bed and walk about the ward with back-brace and crutches. However, her level still persisted at the fourth thoracic dermatome. The neurological signs were essentially the same as on admission. She was discharged on July 18, 1928.

The sections of the tumour removed at operation showed a plasma cell myeloma—"tissue composed of closely packed cells with hyper-chromatic nuclei in which the chromatin is arranged radially in cart-wheel fashion. Some of the nuclei are eccentrically placed. The cytoplasm is pale blue in colour". (Dr. D. Symmers).

The patient improved so rapidly that within two months she was able to walk about and attend to all her duties unassisted. This improvement persisted until February, 1930. She noticed that her legs were getting progressively weaker, and at night her lower extremities would tend to "draw up spontaneously," so that whenever she wanted to turn over she would have to extend them vigorously. There had been no sphincter disturbances. Two weeks before readmission (March, 1930) she tripped in the street.

The neural status was essentially the same as on the first admission: bilateral spastic paraplegia with overactive reflexes and bilateral Babinski

toe signs, and sensory defects in all forms of sensation up to the fifth thoracic dermatome.

Lumbar puncture was again performed, but no fluid was obtained.

Since she had evidently a recurrence of the growth with resultant compression of the cord, laminectomy was performed April 7, 1930 (Dr. D. Klenke). The bodies of the fourth and fifth thoracic vertebræ were soft and mushy and evidently infiltrated by tumour. There was compression and angulation of the cord at this level, so that the entire dural sac was pushed sharply backward by the ventrally placed neoplasm, which extended from the third to the fifth thoracic vertebra. A definite degree of atrophy of the cord was present. As much of the growth as possible was removed.

Sections of the tissue at this time again revealed a plasma-cell myeloma (Dr. Douglas Symmers).

The patient improved greatly after the operation and deep X-ray therapy was again begun. She was able to walk the length of the ward unassisted. On November 12, 1930, there was a sudden onset of acute pain in her back at the level of the operative area with an instantaneous complete paralysis of both lower extremities. Examination showed a complete flaccid paraplegia of the lower extremities with absent deep reflexes and a level at the seventh thoracic dermatome, below which sensation was entirely lost. There was tenderness over the fifth thoracic vertebra. Complete retention of urine and faeces was present. X-rays now showed complete destruction of the fourth and fifth thoracic vertebral bodies. It was not felt that surgical intervention would be of any benefit; she was therefore placed in extension and given routine nursing care.

Repeated X-rays of all the long bones, skull and sternum at this time were negative. Search for Bence-Jones bodies in the urine was again unsuccessful. Her course was gradually downhill. She developed a cystitis, ran a low-grade fever for months, and was transferred to the Central Neurological Hospital, where she died on April 5, 1932.

Autopsy was performed by Dr. Vera Dolgopol. Severe erosion of the third, fourth and fifth thoracic vertebræ was found, as well as erosion of the tenth, eleventh and twelfth thoracic vertebræ. Soft pieces of tumour were found extending into the spinal canal between the softened bones. The spinal cord was atrophic in the upper thoracic segments at the region of the operation. The skull showed no thickening of the bone and no tumour masses could be found in it. Examination of the brain was essentially negative.

The heart was slightly dilated, especially the right ventricle, with intact valves and a somewhat flabby myocardium. The aorta showed atheromatosis. There was lobular pneumonia in the lower lobes of both lungs, with congestion of the bronchi.

Bones: A greyish soft tumour containing hæmorrhagic areas, 4 by 2 cm., was found at the chondral attachment of the left fifth rib. The vertebral parts of both fifth ribs were transformed into tumour tissue by direct extension from the vertebral focus. The right iliac bone crumbled easily: a blood-clot was

seen between the laminae of the iliac bone. The spleen showed moderate congestion with hyperplasia of the pulp. The liver was essentially normal, except for one firm, grey nodule, 2.5 cm. in diameter, in the right lobe. The gall-bladder and pancreas were negative. The kidneys were normal, except for old arteriosclerotic infarcts and adherent capsules. A few retracted scars were seen in the cortex which were regarded as old healed infarcts. The rest of the genito-urinary tract was normal except for a chronic cystitis. The stomach and small intestines showed no pathological change. The colon revealed a pale, slightly indurated ulcerated area 2 cm. in diameter, at about the region of the splenic flexure. A small, firm, white nodule was found in the mesentery near the colonic ulcer.

The final pathological diagnosis was plasma-cell myeloma of the various bony tumours described, and a primary adenocarcinoma of the colon with metastasis to the mesentery and liver.

Case 4.—N. D. (No. 2980), a woman aged 64, was admitted to the medical service of St. Vincent's Hospital, Staten Island, N.Y. (Dr. Herbert A. Cochrane) on August 2, 1932, complaining of pain in the left lumbar region which began two months before admission. It was often sharp in character and radiated across the back and abdomen.

The family and past history were negative except for a left-sided nephrectomy performed in 1905.

The motor power in the lower extremities and control of the bladder and rectum were completely lost. Anaesthesia and analgesia were found below the twelfth thoracic dermatome. A diagnosis of a metastatic spinal tumour was made (September 23, 1932). One week later, Dr. C. C. Hare noted that the sensory level was unchanged, and that the tendon reflexes in the lower extremities were greatly diminished on the right and lost on the left; there was no response on plantar stimulation.

Spinal fluid examination revealed a clear, colourless fluid; manometric readings showed a complete block.

X-ray examination of the genito-urinary tract revealed hypertrophy of the right kidney; there was no evidence of intrathoracic lesion: the sacro-iliac joints were normal. The gastro-intestinal tract showed spasticity of the colon and probably a congenital transduodenal membrane. X-rays of the lower thoracic and lumbar vertebrae revealed spondylitis or possibly trophic disease.

Examination of the blood showed: Hæmoglobin 80 per cent.; red blood-cells 4,760,000; colour index 0.85; white blood-cells 12,000; polynuclears 83 per cent.; small lymphocytes 16 per cent.; large mononuclears 1 per cent.; some degree of anisocytosis was noted. Blood sugar .097 per cent.; urea nitrogen 12.3 mg.; urea 26.3 mg.; uric acid 2.0 mg.; creatinin 1.7 mg.

A number of urine examinations showed a trace of albumin, occasional hyaline and granular casts and an occasional leucocyte and erythrocyte; there

was a pre-agonal acetoneuria. Examination for Bence-Jones bodies was not carried out.

The patient died on October 2, 1932.

The autopsy was performed by Dr. M. Freund.

Microscopical study of the tumour disclosed the picture of a myeloma (fig. 4). The type cells were middle-sized, with large characteristic nuclei, some light, others dark by staining; an occasional cell contained hæmoglobin; dark nucleated red cells were seen. Another type of large cell resembled a megakaryocyte. The stroma of the tumour consisted of fine connective tissue fibres containing numerous capillaries, which were markedly distended. Hæmorrhagic foci were noted. Other sections revealed similar pictures with a larger number of megakaryocytes. Oxydase staining showed that these mononuclear cells were oxydase negative.

The spinal column, at the region of the eleventh thoracic vertebra, was prominent. On palpation, this vertebral body was replaced by soft tissue, which could be removed without any difficulty. The same changes were present in the fourth and fifth ribs on the left side near their vertebral ends. At the point where it passed the eleventh thoracic vertebra, the spinal cord was compressed.

The serosal surface of the bladder showed bluish discoloration; it was distended. The mucosa was dark bluish-red and necrotic. The submucosa was densely infiltrated with polynuclear leucocytes and plasma cells; the infiltration extended to the muscular coat.

The uterus was normal, except for a myofibroma the size of a hazel-nut on the right. The Fallopian tubes were normal. The ovaries were markedly fibrotic.

The cortex of the adrenal was poor in lipoid; the medulla was well developed.

The final pathological diagnosis was multiple myeloma, broncho-pneumonia, cystitis.

Comment.—The age incidence (53 years) of the foregoing three cases was the usual one. In all, the signs pointed to compression of the thoracic cord with manometric block. Bence-Jones bodies were not found in the urine in two of the cases. In two, the X-rays showed evidence of destruction of a vertebral body. In four of Klemme's five cases there were no X-ray changes; on the other hand, in one of the cases reported by Jacox and Kahn the destruction of the third lumbar vertebra finally became so complete as to lead to the disappearance of the vertebra. In the first case of the man still alive, we are dealing with a myeloma which is as yet solitary. In the second and third cases the myelomatous process was relatively circumscribed to vertebræ and adjacent ribs. The duration of the illness was well illustrated by the second and third cases—fifty-two months in one, four months in the other. The terminal infections in the bladder and lung need no comment. The presence of an

associated adenocarcinoma of the colon with mesenteric and hepatic metastasis came as a complete surprise in the post-mortem of the second case.

The spinal signs in cases of myeloma are not always due to pressure from the neighbouring growth. Nonne [21] reported the case of a man aged 57 who was taken ill with severe pains in the neck and arms; muscle atrophy in the ulnar parts of the hands, miosis, priapism and tenderness on pressure of the lower cervical spine developed and pointed to a "cervical meningomyelitis." X-rays revealed rarefaction and shrinkage of the first thoracic vertebra. Cachexia set in rapidly and death occurred in two months. The vertebral lesion was a myeloma. Microscopical study showed no demonstrable cord lesion. Nonne believed that a toxic effect was produced on the cord by the neighbouring myeloma. Kreuzer [22] described multiple focal degenerations in the dorso-lateral white matter of the spinal cord, especially marked in the ninth and tenth thoracic segments, which he believed followed hæmorrhages. Since autopsy revealed a myeloma of the fourth and fifth thoracic vertebral bodies, this author concluded that the distant effects of the tumour on the cord could not be caused by mechanical pressure but were due to the action of the toxin.

Conclusion.—Four instances of myeloma are described with neurological complications. The first is an example of the generalized form of the disease. The other three illustrate the vertebral type in which the myeloma is circumscribed to vertebral and extradural tissues at the time of the rapid development of signs of spinal cord compression. The upper thoracic cord is usually the part involved. The patient is generally in the fifth or sixth decade of life. X-rays may show destruction of the diseased vertebra. Laminectomy reveals a reddish-grey extradural growth, removal of which is followed by great, if temporary, improvement. Deep X-ray therapy and the wearing of a back-brace are advised after laminectomy.

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EFFECTS OF EXPERIMENTAL LESIONS OF THE POSTERIOR COLUMNS IN *MACACUS RHESUS* MONKEYS.

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I.—INTRODUCTION.

ALTHOUGH it is generally assumed in textbooks on clinical neurology that the functions of the dorsal columns are well known, being essentially those concerned with the transmission of the more discriminative types of sensibilities, it is remarkable how few experiments have been performed in animals on the dorsal column system, especially in forms such as the monkey. To be sure, most of our knowledge concerning the physiopathology of the dorsal columns has been obtained from human cases. However, in such cases the lesions are usually not well circumscribed and not confined alone to the dorsal column system. In tabes, for example, there is usually an involvement of dorsal roots in addition to that of the dorsal columns, and in tumours or traumatic conditions the extent of the involvement is also generally greater than the posterior columns themselves. In other diseases involving the dorsal columns, such as multiple sclerosis, combined sclerosis and degenerative or other diseases, the pathological process is rarely, if ever, confined entirely to the dorsal columns, and it seemed of interest to us, therefore, to investigate experimentally the function of the dorsal column system as the first step in an analysis of the effects of lesions at various points in the sensory system.

Even when one reviews the experimental work performed by physiologists on the dorsal columns and the dorsal column nuclei in the medulla one finds very few uncomplicated cases where the experimental lesion was confined entirely to the dorsal columns or their nuclei. In addition, many of the earlier experiments were performed merely as acute experiments and little was learned concerning the ability of the animal to engage in its daily activity and of its ability to compensate for the loss of function of the dorsal column. In most of the earlier work unsatisfactory anatomical controls were reported, and in cases where more than gross anatomical reports were given in adequate

drawings were presented. On the other hand, much of the earlier work was concerned with the effects of lesions, or removal, of the dorsal columns in the thoracic region, not therefore involving the anterior limbs; whereas, we feel, that the most interesting result from a clinico-physiological standpoint is that following the lesion of the posterior column in the cervical cord, which involves, especially in the higher types of animals, both front and hind limbs.

It has been our purpose, therefore, to establish first of all the anatomical relationships of the dorsal columns and dorsal column nuclei. This is being reported at length elsewhere. On the basis of these anatomical findings, we have hoped to explain the symptomatology resulting from lesions at the different levels of the dorsal column system, particularly of the cervical region, and from lesions of the dorsal column nuclei. A large series of animals has been operated upon to obtain these results. All have been carefully controlled anatomically and the behaviour of the animals recorded by moving pictures at various, acute stages up to the chronic stages of many months.

II.—REVIEW OF LITERATURE.

Numerous early authors were concerned with the functions of the dorsal columns from the standpoint of conduction of various types of sensation. Bell [1], for example, believed that the dorsal columns conducted practically all forms of sensation to the brain, in contrast with the anterior columns which conducted motor impulses towards the spinal cord.

On the other hand, Bellinger [2] and others found no disturbances in sensation after cutting the dorsal columns, whereas Longet [3], Van Deen [4], Fodera [5], Magendie [6], and others supported Bell's general findings.

Brown-Séquard [7] found complete anæsthesia below the region in animals following lesions of the spinal cord in cases in which the dorsal spinal columns were spared. He explained the difference in his findings from those of Longet by the fact that in his experiments the grey substance remained intact. Brown-Séquard believed that the grey substance of the cord carried sensations and that when this was cut the anæsthesia occurred.

The work of Schiff (1857) [8, 9] determined opinions in neurophysiology for many years. He believed that, in general, the dorsal column is the sensory path for various deep sensibilities. Since this is the main path, loss of the dorsal column cannot be compensated to any

great extent. He believed that section of the dorsal column causes a permanent loss of deep sensibilities, that the sense of position is only a function of the tactile sensibilities, and that the loss of sense of position following lesion of the dorsal columns is really due to or based upon the loss of touch and that the two are usually involved in the same degree. In his animals he stated as evidence of the loss of sense of position that the animals slide the feet along, especially if the floor is uneven. The dogs lift their feet to various abnormal degrees on running, sometimes too much and sometimes too little. Schiff maintained that the symptoms observed by him in the dog were essentially those described by Fritsch and Hitzig after removal of the cortical area described previously by Munk as the sensory sphere. Schiff compared the findings in his animals with those following cortical lesions and, based upon the similarity in symptomatology, postulated a course of the dorsal columns to the cortex. He thought that partial compensation occurs in the animals, for example a wider spreading of the toes which prevents the animal from turning the foot over with the dorsum downward, an occurrence observed in the early stages following the operations. Likewise, the animal could compensate to some extent by increasing the pressure of the foot on the ground on walking, thus allowing harder pressure to compensate to some extent for the deficiency of touch. Schiff considered that pain was conducted in the grey matter, whereas the white substance of the dorsal columns was considered as primarily concerned with the tactile stimuli.

Von Leyden (1863) [10] described symptoms in animals similar to those of Schiff and confirmed his work in the main points.

Ewald (1898) [11] removed about 7 cm. of the dorsal columns from the thoracic region of a dog and described, in addition to what he termed a motor ataxia in the hind limbs, a tactile and thermal anæsthesia in the animal below the lesion. The sense of pain did not appear to be diminished. The ataxia in the hind limbs improved greatly, and several months after the lesion, little, if any, abnormality in the sensory-motor sphere could be found. The touch and temperature loss, however, remained.

Türk [12] found a swaying gait and some anæsthesia distal to the lesion of the dorsal columns in lower animals such as the rabbit. This persisted only for a short time, and there was no marked cutaneous sensory loss.

Munk [13] developed his "Berührung" reflex as evidence of intact cortical representation. To elicit this reflex the animal was suspended

in the air by the neck and trunk with the legs hanging free and the eyes shielded. Light touch on a limb usually called forth a prompt moving of the limb away from the stimulus. This disappeared following lesions of the sensory sphere and also of the dorsal column system.

Bickel (1898) [14] removed a portion of the dorsal columns in the thoracic region of a dog, and reported a long-lasting sensory deficiency with ataxic symptoms in the hind limbs. The ataxia disappeared before the sensory loss. He believed that one of the main functions of the dorsal column was the conduction of "muscle sense." Pain and temperature were not lost.

Martinotti (1890) [15] found no disturbance of movement and sensation after section of the dorsal columns.

Borchert (1902) [16] reported the effects of lesions of the dorsal columns in thirteen dogs. Lesions were made in the region of the thoracic and cervical cord. He found the sense of touch (*Berührungsgefühl*) and the response of pain retained. The sense of position (*Lagegefühl*) was not lost in pure cases. In cases, however, where the lateral columns were also involved there was also a loss of sense of position. Equilibrium usually showed no abnormality. Pure cases usually showed no other type of abnormality, except for a slight temporary disturbance of gait in the animal. No marked disturbances were seen in gait or in the finer isolated movements. These results, according to Borchert, were to be contrasted with the findings of Schiff and were more in agreement with the physiology of man. In man, according to Borchert, there may be retention of touch even with degeneration of the dorsal columns. Touch must therefore be considered as being carried along other pathways, probably of the second or higher order, but not along the long ascending first order fibres of the dorsal columns. It is possible, according to Borchert, that there is some diminution in the sense of touch, but it is rather qualitative than quantitative. We may note that only two of Borchert's animals, in one of which the lesion was performed in the cervical region, appeared from the author's report to be pure cases. The others usually showed some complicating lesions, particularly injury of the lateral columns.

Borowikow [17] found after cutting the dorsal columns that touch (*Berührungsgefühl*) was retained, but that "muscle sense" disappeared or was considerably diminished. In addition, general equilibrium and co-ordination of the movement appeared to be destroyed.

Bechterew [18, 19] felt that the main criticisms of Schiff's work can be based upon two points.

(1) On the absence of microscopical controls which would probably have revealed in most cases a simultaneous lesion of the lateral columns.

(2) On poor and inadequate methods for testing the various types of loss, especially the type of touch loss supposedly associated with cortical reception. For this Schiff used the reaction to tactile stimuli, which, according to Bechterew, is in all probability a reflex not requiring the cortex for its elaboration.

Bechterew reported observations on section of the dorsal columns in pigeons, rabbits and dogs, in the cervical region. In general, he found evidence of disturbance of equilibrium and co-ordination. In animals in which he checked the lesion microscopically, and in which there was a lesion of the dorsal columns, there was usually a loss of muscle sense and involvement of tactile sensation associated with ataxia. Many of these animals he described as showing the ataxic gait of tabes. In his animal protocols he describes, for example, in a lesion at the level of the fourth thoracic vertebra, a side to side swaying of the body. The movements of the hind limbs appeared somewhat difficult and the swaying increased when the eyes were closed. There were no symptoms of paralysis. Bechterew concluded on the basis of his own and similar experiments performed by Cudnowski in his laboratory, that the dorsal column undoubtedly conducts muscle sense and in part tactile sensibility. With time the disturbance of the sense of position and of movement decreased, and after six weeks the animals appeared entirely normal. The sense of pain was usually completely retained, but thermal sensibility was changed. He reported one case in which unilateral section of the column was made, and in this case disturbance in position and movement occurred only on the side of the lesion, or possibly to a slight degree on the other side. He concluded from this that the major conduction of muscle sense is uncrossed in the dorsal columns. The tendon reflexes were retained in all experiments in all animals operated upon even if the section were performed in the upper lumbar cord. Bechterew concluded, therefore, that the paths associated with tendon reflexes took a short, if any, course in the dorsal columns. Since the work of Bechterew practically no experiments have been reported on the effects of lesions of the dorsal columns.

In man most of the lesions of the dorsal columns have been performed by nature, and in the standard textbooks on neurology, such as that of Tilney and Riley [20], one may find the statement that the function of the dorsal column is the transmission of impulses associated with various discriminative forms of sensation, including that of position

and movement, discriminative touch, &c. It may be of interest here, however, to mention the work of Kroll [21], in which section of the dorsal columns in man was associated with a definite diminution in the number of pressure spots on the skin below the lesion. Foerster and Gagel [22] found evidence that some transmission of pain possibly occurred through the dorsal columns in a small aberrant bundle of fibres which bends out of the antero-lateral column.

Experiments on stimulation of the dorsal columns, in which numerous reflex movements were obtained by workers such as Van Deen, Longet, Brown-Séquard and others, may be dismissed on the ground that improper localization and control of the stimulation both as to intensity and extent make such experiments of little value as evidence of the normal functions of the dorsal columns.

In our survey of the literature we have been unable to find any reference to the effects of lesions of the dorsal columns in monkeys or in the higher apes.

III.—EXPERIMENTAL MATERIAL.

Macacus rhesus monkeys, averaging from 8 to 10 lbs., were used in the experiments. They were subjected to no special training before the operations. All operations were performed under ether anæsthesia and with aseptic technique. The operations were done as simply and rapidly as was consistent with obtaining the desired result. The levels at which lesions were made were the fourth or fifth cervical segments and the mid-thoracic region, so as to involve respectively both lower and upper extremities or only the lower extremities, and in the upper lumbar region. After removal of two or three vertebral laminae at the level chosen for the lesion the dura was split in the midline, the arachnoid carefully removed. The dorsal columns usually could be well seen between the dorsomedial lines of attachment of the entering dorsal roots. Before making the lesion the dorsal vessel of the cord was usually freed with its arachnoid from the cord and retracted, thus being spared in the lesion. When the purpose of the lesion was completely to destroy the dorsal columns, the actual cut was made with an arrow-shaped knife, sufficient in size to sever the columns completely at the level chosen. Occasionally, however, the lesions were made with a small Bard-Parker knife, using a blade No. 11. The columns were usually simply sectioned and none of the dorsal column substance was removed. In most cases a mark was made on the blade to indicate the depth to which the knife would have to go in order to complete the section. Usually very little bleeding occurred following the lesion and

very little swelling of the cord took place immediately after the section. In general the dura was not closed since it was found in a few earlier experiments that the fine black silk sutures used to close the dura occasionally produced additional secondary cord lesions. The muscles were approximated with silk or catgut sutures and the wound closed with Michel skin clips. The wound was simply dressed with iodine followed by powdered boric acid. No bandage of any type was used. With such simple methods, good lesions were generally obtained. No infections occurred in a series of over twenty monkeys, and in no case was the wound opened either by trauma or by the monkey itself.

The animals were observed while coming out of the anaesthesia. They usually had recovered completely by one hour after the end of the operation. The first complete examinations of the animals were made at the three-hour stage when the effects of the anaesthesia had apparently completely disappeared. Subsequent observations were made daily up to the time of sacrifice of the animals. In monkeys which were studied by the Marchi method, the animals were sacrificed from about the twelfth to the sixteenth day. Immediately after death from ether the animals were perfused with 50 per cent. formalin through the aorta, and brain and cord embedded and stained according to the technique advised by A. T. Rasmussen [23]. In general excellent results were obtained with the Marchi stain. Serial sections of the lesion and of sections of the cord at various levels above and below the lesion were made. In particular, the termination of the degenerated portions of the dorsal columns in the medulla were studied serially. Other animals were studied by the Weigert method; some were allowed to live for various periods, some well over six months, in order to observe the improvement which occurred and to allow subsequent operations on other portions of the sensory system, and in them the usual Weigert technique was used.

Moving pictures were taken to illustrate all of the characteristic features of each animal both in the acute and chronic stages. In general, a complete neurological examination was performed on every animal. This consisted of careful observation of the spontaneous behaviour of the animal both as regarded posture and locomotion on the ground and in climbing about the cage. Usage of the limbs, muscle tone, deep reflexes including the arm and knee jerks, the condition of the grip, the ability to climb along a bar, the ability to jump and swim, the special reflexes including hopping, placing, falling and righting reflexes and the various labyrinthine position reflexes studied by Magnus in his vestibular animals were all carefully investigated on each animal.

In order to demonstrate the characteristic symptoms, a typical protocol from each operation will now be presented. These include an animal with a complete section of the dorsal columns at the fourth cervical segment, an animal with section of the columns of Burdach alone at the fourth cervical segment, an animal with complete section of the dorsal columns, and therefore essentially the columns of Goll, at the seventh thoracic segment, and finally an animal with section of the dorsal columns in the upper lumbar region.

Protocol No. 1.—Monkey Cer. 80, January 12, 1933.

Operation: Complete section of the dorsal columns at the fourth cervical segment. As the animal was coming out of the anæsthesia it showed marked generalized inco-ordination, falling about to one or the other side, and random movements of the limbs with relatively little use of the fore limbs. Each time it made some effort to stand it fell over quickly to one or the other side.

Three hours after operation.—The animal was well out of the anæsthetic. There was seen to be a very marked general disability. It preferred to lie in the cage, making feeble efforts occasionally to stand but not succeeding very well. Its posture was predominantly that of flexion. The fore-limbs were held flexed at the elbow in almost a hemiplegic position with flexion at the wrist. No effort was made to use the limbs spontaneously. The hind limbs were held in a more extended position but very slight co-ordinated movements were made with these limbs. The animal made no successful attempt to climb about the cage at this stage. It appeared not to know what to do with the limbs. An attempt to induce it to grasp the wire sides of the cage was unsuccessful. When dropped head first, with eyes open, only very slight movements of extension were made with the limbs. Placing and hopping reflexes were completely absent in both front and hind limbs. The animal could not right itself when placed on its back. An attempt was made to right the monkey by rotation of the head toward one or the other side, but in no case did the limbs follow the head successfully. So far as could be determined roughly, the animal could feel touch and pain. This was tested by holding the animal so as to cut off the visual element and then watching the eyes while one of the observers either pinched the animal or pricked it with a pin. Movements of the eyes in response to this were observed. It thus appeared that the animal could feel pain and also could feel touch. When the limbs were moved slowly, how-

ever, under similar conditions, the animal appeared to be unaware of this and made no attempts to oppose the change in position of the limbs. This was especially true if the changes in position were made slowly so as not to transmit the sense of movement to too large a portion of the body.

Muscle tone showed a definite decrease in all four limbs. This diminution appeared even greater in the front limbs, although the diminution in the hind limbs was very definite and of a marked degree. Deep reflexes on the other hand were very active. The knee-jerk appeared pendular and very active, possibly even more active than the normal knee-jerk in the monkey.

January 13, 1933: Twenty-four hours after operation.—The condition of the animal was still essentially the same, except for the fact that it attempted to right itself more often and made rather ineffectual efforts to move about the cage.

January 17, 1933: Five days after operation.—During the past four days the animal made more and more attempts to right itself and use the limbs to some extent. To-day, however, was the first day in which the animal sat up successfully. As yet it has shown no ability to use the fore limbs as single flexible prehensile organs, all food being taken directly into the mouth. The difference in the ability to use the front and hind limbs has been shown during the past few days by the animal occasionally moving itself about the cage by a pushing movement with the hind limbs. The front limbs always remained adducted and in the semiflexed and motionless posture. The hands were open and no flexion of fingers was noticed. These were not used at all for any type of movement of support and it appears that the animal was not aware that it had front legs. In sitting the hind legs were widely abducted without the flexion attitude which was so marked in the front limbs. The animal when placed upon the floor made feeble efforts to move about. When it attempted to stand up it did so only on the two hind limbs with a very broad base. The only movements made by the animal consisted of slight attempts at hopping along the ground and also occasional jumping, which was done entirely with the hind legs. When the animal jumped, however, it fell over to one or the other side and never made well co-ordinated jumps using all limbs. When the animal was held up against the cage to test its ability in climbing, it could not grasp the wire cage with its forelimbs. The same thing occurred when the animal was placed on the horizontal bar and allowed to drop. The only movements observed

then consisted of gross types of supporting movements made almost entirely with the proximal portions of the limbs. No attempts were made to grasp the bar actively with either the front or the hind limbs. All the special reflexes, including hopping, placing and position reflexes, were as reported at the three-hour stage. The righting reflex had apparently returned to some extent as the animal could now turn over on to its stomach, by coarse, poorly co-ordinated movements when placed on its side. The head, however, appeared to be well oriented in space as all position reflexes on the head appeared normal. Muscle tone persisted definitely diminished. Deep reflexes similarly remained active.

The chief elements in the picture at this period, which might be classified as typical of the acute stage, were the absence of spontaneous movements of the prehensile type in all limbs, especially marked in the fore limbs, loss of the sense of position as tested by slow movement of the limbs, the characteristic posture in the front limbs, the absence of spontaneous grip in all limbs, the generalized hypotonia, the retention of response to pain and deep touch with the absence of the placing and hopping reflexes, and finally the retention of good active knee-jerks.

January 26, 1933: Two weeks' stage.—The animal had made slow improvement since the fifth day. The most marked improvement was in its attempts to walk, which it does fairly well at the present time. The animal walked about entirely with the hind limbs, the gait being essentially hopping, resembling the gait of a kangaroo, the front limbs being held in a fairly flexed posture, hypotonic and useless, at the sides. When the animal made any efforts to use the front limbs in walking it usually fell over, since no well co-ordinated movements could be made with these limbs. However, it jumped about remarkably well, the hind limbs showing considerable spring, with, however, rather poor co-ordination on the part of the rest of the body. For example, if the animal attempted to jump into its cage from the floor it usually jumped too far or too much to one side, thus missing its goal.

When the animal was placed on the horizontal bar to-day, it was able to hang there by supporting itself entirely with the proximal portions of the limbs, that is the upper arms and the thighs. When attempts were made by the monkey to grasp the bar, the grasping was done almost entirely with the proximal portions of the limbs, and even if some other object such as a bar were brought toward the animal, the animal made groping movements with the limbs without actually grasping the bar actively. If, however, the feet or hands of the animal were

placed around the bar and the animal was then allowed suddenly to drop, it failed to support its weight. As yet the animal has made no attempt to feed itself with the hands, always reaching over with its head to pick up food. Sensory responses have been consistent in showing a retention of pain and touch and a definite loss or marked diminution in the sense of position. The main improvement during the past ten days has been the development of a hopping gait, mainly with the use of the hind limbs. Otherwise the main deficiencies in this animal, the inability to grip, lack of spontaneous prehensile type of movements, the loss of sense of position, the hypotonia, and the sensory loss, have remained the same.

February 12, 1933: One month after operation.—The animal has now developed a satisfactory gait, but with a tendency to retention of hopping, using mainly the hind limbs. During the past week it has to some extent used the front limbs in walking. These were rather clumsily used with a tendency towards slipping out to one or the other side. The front and the hind limbs showed a tendency to place in walking the dorsum of the foot against the floor. This has not been so noticeable in the hind limbs as in the front limbs. The characteristic loss of spontaneous grasping movements, especially with the front limbs, have still persisted. The hands, however, have been used to a slight extent during the past three or four days, in bringing food to the mouth, and in sliding the food along the floor of the cage. As yet the animal has shown no ability to reach out and grasp food with the fingers as a normal animal would do. The arm has been used as an implement to direct or support the food on its way to the mouth. Fine movements of the fingers have been absent.

When examined to-day the animal showed some ability to climb along the bar, never, however, upon the bar, but always hanging below it. The proximal segment type of support as previously described still remained. If the animal were teased with a stick, vague defensive movements were made in which the animal warded off the stick with the fore arm or with the upper arm without actually grasping the stick with the hand as a normal monkey would do.

The animal retained, however, some power to hang suspended from a bar, especially if the hands were placed around the bar first and then the animal was allowed to drop suddenly. Responses to pain and deep touch were still as described at the earlier stage and the animal still failed to notice slight slow changes in the positions of the limbs. Muscle tone was definitely diminished in all limbs and the deep reflexes still

were good. If the animal were placed up against the wall of the cage it showed some ability to grasp the wall of the cage with all four limbs, although the grasp with the front limbs was definitely deficient. Once the animal had succeeded in grasping hold of the cage, it apparently could go no further. Coördinated movements of climbing were absent.

When the animal was placed in a tank of water for a swim it showed rhythmic movements in all limbs and it did not appear in danger of drowning like a monkey with loss of vestibular function. This was probably due to the fact that the animal could keep its head oriented in the water, whereas the vestibular monkey could not.

April 12, 1933: Three months after operation.—The animal during the past two months has continued to improve slowly, especially with regard to the use of its limbs. The front limbs still have shown much more defect than the hind limbs. Incomplete coarse grasping movements have become possible. The animal has improved in its ability to use the limbs in bringing the food to its mouth. During the past month it has learned to sit up in the corner of the cage with the front limbs resting on the sides of the cage. During the past two months the animal has learned to jump about remarkably well, and the front limbs have also been used more in locomotion. The main deficiencies when the animal walked have been the lack of spring in the front legs and the constant slipping out of the limbs with the tendency to walk on the dorsum of the foot. It has shown some power to climb along under the bar, although the firm, precise, co-ordinated grasping of the bar with the digits of the front or hind feet has been impossible. It has only been during the past two weeks that the animal has shown definite improvement with regard to the use of the hands. At the present we may say that the predominant elements in the picture are the relative inability of the animal to climb about while hanging on the sides of the cage; a definite loss of the sense of position in the limbs as manifested by the occasional passive acceptance of abnormal postures such as walking on the dorsum of the foot, and the persisting hypotonia with active reflexes. The chief defect in the limbs is probably a loss of sense of position and movement.

July 12, 1933: Six months after operation.—The animal reached its stage of maximum improvement between the third and fourth month when it attained some ability to climb about on the cage. Walking, however, still retained the hopping character. More definite grasping movements had become possible with the front and hind limbs. The animal reached for food and brought it to the mouth, although these

movements were rather coarsely executed. The hypotonia still persisted. The deep reflexes appeared exaggerated, but the hopping and placing reflexes returned to some extent at about the third or fourth month, especially when the animal was tested with the eyes open. It is of interest that when the animal was allowed to walk about or jump about with the eyes blindfolded there was a considerable increase in its deficiencies. The front limbs tended to return to their original flexion posture.

The main points which characterized the animal at this stage

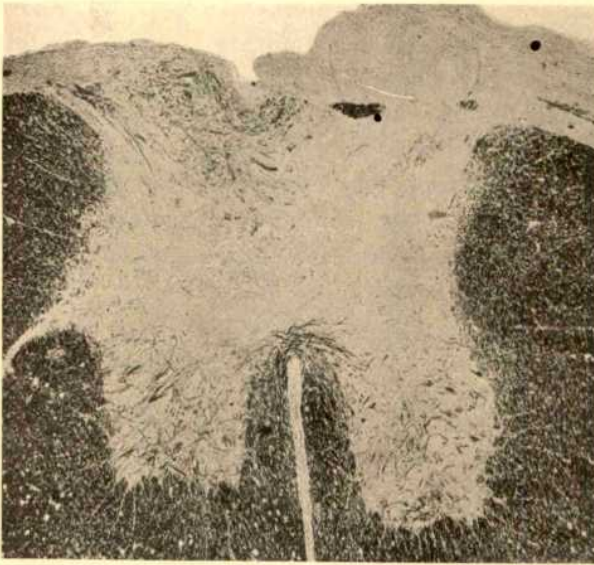


FIG. 1.—Section of the cervical cord at approximately one-half segment above the level of section of the dorsal columns showing the complete degeneration of the dorsal columns. Weigert preparation.

were deficiency in spontaneous fine grasping movements and in fine co-ordinated movements of the limbs as in climbing along under a bar, a clumsiness and stumbling in fast movements, a lack of spring in the limbs, especially in the front limbs, in jumping, with a tendency toward spreading of the limbs, a persistent hypotonia with active deep reflexes and, finally, a retention of pain and touch sensibilities. All of the deficiencies increased when the animal was blindfolded.

Two weeks later the animal was killed and perfused with formalin to be studied in serial sections with Weigert's stain.

Anatomical Study.

Macroscopically, the lesion is confined to the fourth cervical segment. There is a slight amount of scar tissue on the dorsal aspect of the cord. The remaining portion of the cord above and the whole cord below the lesion appear of normal size with no other evident abnormality. Histologically the lesion is found to have completely severed the dorsal columns at the level of the fourth cervical segment. Below the lesion there is no evidence of involvement of the pyramidal tract. Above the lesion the degeneration of the dorsal columns is seen to be complete and there is no evidence of involvement of the dorsal-spino-cerebellar tracts. The degeneration of the dorsal columns immediately above the lesion can be seen from fig. 1. The degeneration can be easily followed to the termination of the columns in the nuclei of Goll and Burdach in the medulla. The anatomical picture just described is typical of complete lesions of the dorsal columns in the cervical region. In other cases where the Marchi method has been used, similar pictures showing complete degeneration of the columns at the level of the lesion and subsequent degeneration to the termination in the medulla could be easily followed.

Protocol No. 2, Cer. 82: February 13, 1933.

Operation: A lesion was made at the fourth cervical segment so as to divide both columns of Burdach. The most medial point of the lesions coincided on the dorsal aspect of the cord with the dorso-lateral sulci.

Immediately after operation the animal showed a severe hypotonus of the front limbs and weakness of these limbs with relatively little motion. When the animal was coming out of the anæsthesia the hind limbs were moved vigorously and frequently. No general postural defects could be seen.

Three hours after operation.—The animal was well out of anæsthesia, and was sitting up in the cage. There was relatively little involvement of the hind limbs. The abnormality seemed to be confined to the front limbs. The animal when sitting up held the front limbs in a flexed position resembling that of Cer. 80 in Protocol No. 1, described above. The hind limbs apparently retained essentially normal posture and the animal used them quite freely. In gait the animal showed a great difference as compared to Cer. 80. In the first place, the hind legs seemed to be relatively slightly involved, apart from a slight general instability and tendency to stumble when the animal was moving fast.

The animal walked about and even the involvement of the front limbs appeared to be slightly less than might have been expected from complete lesions of the columns of Burdach, assuming that the columns of Burdach contain the whole afferent proprioceptive nerve supply from the upper limbs. The front limbs were used to a slight extent in walking. When the animal attempted to walk on all fours, the movement in the hind legs appeared entirely normal, but those of the front legs appeared very deficient. There was slipping out of the front limbs, marked uncertainty in every position, and a tendency for the animal to walk on the dorsa of the feet. The grip in the front limbs was absent, that in the hind limbs was relatively well preserved. When jumping for the cage or attempting to jump up the side of the cage, the animal showed a complete lack of ability to climb with progressive movements of the front limbs. It could not hold on to the cage. The hind limbs obtained a good grip on the wall of the cage, and if the animal were allowed to drop it hung successfully by the hind legs with head down. The animal could hang from the bar by the hind limbs but not by the front limbs. The muscle tone in the front legs appeared definitely diminished. The deep reflexes were active. The muscle tone in the hind limbs was normal. The animal responded to pain or touch on practically every portion of the body, including the upper extremities and trunk. With vision excluded, the animal made no attempt to correct positions impressed upon the front limbs, but did so immediately in the case of hind limbs. The hopping and placing reflexes were absent in the front legs and present in the hind legs. No abnormal vestibular reflexes were present.

February 14, 1933: Twenty-four hours after operation.—The general condition of the animal was still essentially the same except that it has been moving about the cage and that it has been using the upper extremities slightly to bring food toward the mouth. The movements were essentially those of support for the food rather than active grasping. The general involvement of the animal does not seem to be as severe as in the animal in which the entire dorsal columns were severed at the same level. This is due to the fact that the operation was confined almost entirely to section of fibres from the upper limbs. Therefore, the trunk and the hind limbs are relatively normal. The occasional stumbling and clumsiness and ataxia in the hind limbs is not very marked.

February 21, 1933: One week after operation.—The animal has improved considerably, especially in walking and jumping. It could jump

accurately into the cage and could use the hind limbs for movements of prehension. In taking food the fore limbs were used to support it rather than to grasp it accurately. The grip of the front limbs was poor except when the object to be grasped was firmly placed in the hand and the animal was allowed to drop or was suddenly startled. The animal has not as yet shown any ability to climb up the side of the cage except with the hind limbs. The front limbs were still relatively useless for active climbing. The muscle tone was decreased. The sense of position was definitely diminished in the front limbs, whereas touch and pain were

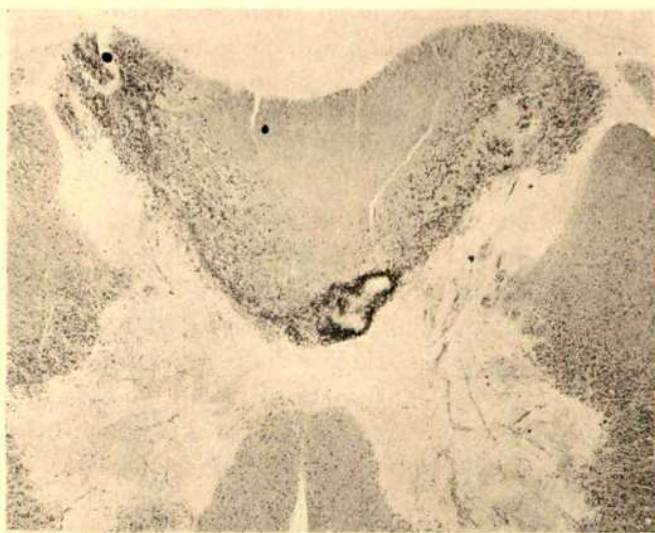


FIG. 2.—Section of the cervical cord at approximately the level of the lesion showing involvement of both columns of Burdach in a practically symmetrical lesion. The columns of Goll are free, as is the grey matter. Marchi preparation.

retained over the trunk and fore and hind limbs. The symptoms were essentially symmetrical in the fore limbs.

February 27, 1933: Two weeks after operation.—The essential findings have remained the same with some improvements in the use of the front limbs. As yet they have not been used successfully for active fine grasping movements or in climbing up the side of the wire cage. Spontaneous grasping has not returned to any great extent. The hind limbs appear now to be relatively free from any abnormality. The defects seem to be confined to the upper extremities where the involvement is relatively severe, consisting of the defects noted above with retention of deep reflexes and deep touch and pain sensations. The

special reflexes, including the extension of the limbs on righting of the animal, are not very active. On dropping the animal, head first, with eyes covered, there is slight extension of the front limbs.

Anatomical Study.

The animal was killed with ether and perfused with 50 per cent. formalin. The spinal cord shows a macroscopic lesion at the level of the fourth cervical segment, in the area of the dorsal columns. Histologically, the lesions are seen to involve both columns of Burdach at the same level. Fig. 2 shows the level of the lesion and fig. 3 the

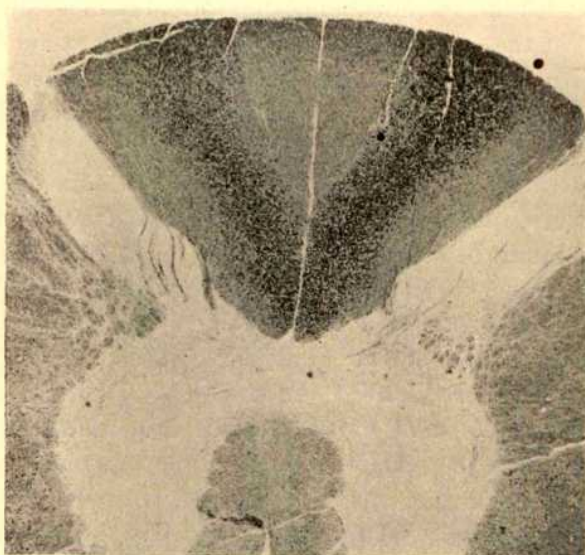


FIG. 3.—Section of the cervical cord at approximately two segments higher than the level of fig. 2, showing the ascending degeneration in the columns of Burdach. The degeneration is seen to be symmetrical. The normal fibres which entered above the lesion are seen ventrolateral to the degenerating ascending fibres. The columns of Goll are free. Marchi preparation.

degeneration involving both columns of Burdach about a segment above it. This degeneration can be traced to the termination of the columns of Burdach in the nuclei of Burdach proper and the nuclei of Clarke-Monakow. Sections taken below the lesion show no evidence of degeneration of the pyramidal tract.

Protocol No. 3, Cer. 135. August 11, 1933.

Operation: Section of the dorsal columns at approximately the seventh thoracic segment. After the lesion there was slight swelling of the cord, with some bleeding.

Immediately after the operation, when the animal was coming out of the anæsthesia, there appeared to be a marked degree of weakness and disuse in the hind limbs which appeared flaccid and were not moved to any extent as compared to the relatively normal movements of the front limbs. No asymmetry in posture was present.

Three hours after operation.—With the animal well out of anæsthesia, the symptoms were confined to the hind limbs, the front limbs being normal except for a certain degree of instability or clumsiness on walking, which seemed dependent upon the relative uselessness of the hind limbs. The hind limbs showed a marked absence of spontaneous purposeful movements, and they often assumed slightly flexed postures both at the thigh and knee. With vision excluded, relatively abnormal postures of the limbs could be superimposed without the animal attempting to correct them. Changes of position likewise could be imposed without any apparent notice on the part of the animal. The animal, with vision excluded, responded with movement to deep pin prick, pinching, and pressure on the hind limbs. When it attempted to right itself after being placed upon the back, incoördinated movements of a coarse type were performed with the hind limbs. Movements of the front limbs appeared normal. When the animal was made to walk a marked weakness of the hind legs could be seen. There was a tendency to drag these legs and to walk with a wide base. Muscle tone was diminished in the hind limbs, but the deep reflexes were active. When the animal was made to climb on the side of the cage normal grasping and climbing movements were made with the front limbs, but the hind limbs were dragged and used clumsily. There was very little spontaneous grasping with the hind limbs. Hopping and placing reflexes were absent in the hind limbs and present in front limbs. In falling with the eyes closed extension of the hind limbs occurred but was slight in degree.

August 12, 1933: Twenty-four-hour stage.—Essentially the same findings were present to-day with the difference that the animal stood up on the hind limbs and apparently had comparatively more use of these limbs than had the previous animal of its front limbs following section of the columns of Burdach. The animal still showed loss or marked diminution of the sense of position and of ability to grasp things accurately and spontaneously. Sensory examination revealed the same type of involvement as before. The animal used the hind limbs progressively in walking on all fours, but stood and walked with the toes of the hind feet bent under. The front limbs were free from abnor-

mality. The diminution in muscle tone and the active knee-jerks persisted in the hind limbs. It climbed along quite readily under a bar with the front limbs and showed some ability to hang with the hind legs, but the hanging was done with the proximal parts of the limb rather than with the feet. The tail showed a diminution in balancing movements and in the wrapping of the tail around the wrist on contact.

August 18, 1933: One week after operation.—The animal has improved rapidly. It now walks with ataxia, and shows a deficiency in spontaneous grasping movements. The sensory and other reflexes have

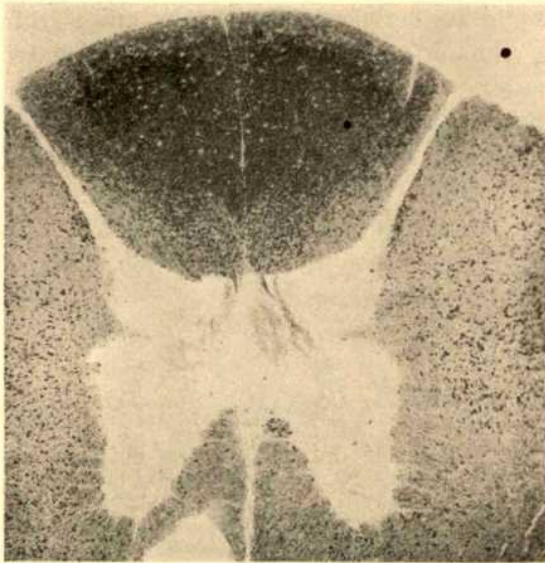


FIG. 4.—Section of the thoracic cord one segment above the level of the lesion in the dorsal columns at the 7th thoracic segment, showing complete degeneration in the dorsal columns at this level. Marchi preparation.

remained unchanged. Muscle tone is diminished in the hind limbs. The knee-jerks are active.

August 25, 1933: Two weeks after operation.—It is difficult at this stage to compare the intensity of involvement of the hind limbs with that of the front limbs following the lesion of the column of Burdach. The involvement is not as marked, and the limbs seemed to be used moderately well but with some incoördination. There is diminution of the sense of position, hypotonia, and a tendency towards abduction on walking. The limbs are not used successfully as prehensile organs. Such acts as climbing are done with the proximal parts of the limbs.

The postural defect which was obvious in the upper limbs when the cervical segments were injured was not present at this stage in the lower limbs. The animal was able to employ its hind limbs in standing and walking, and the hopping and placing reflexes, which were absent for a long period after section of the fibres of the dorsal columns from the upper extremities, returned earlier in this animal.

Anatomical Study.

The animal was killed for study with serial Marchi sections. The lesion was found to be between the seventh and eighth thoracic segments, involving the dorsal aspect of the cord and extending slightly into the grey matter to involve some of the cells of Clarke's column. This produced some ascending degeneration in the dorsal spinocerebellar tracts, which are not directly involved by the lesion. There is no degeneration below the lesion in the pyramidal tracts. The degeneration can be followed upward to the termination of the nuclei in the medulla. Fig. 4 shows the degeneration in the dorsal columns about one segment above the lesion.

Protocol No. 4, Cer. 110. June 17, 1933.

Operation: Section of the dorsal columns between the L 1 and L 2 segments.

Three hours after operation.—The behaviour of this animal resembles so closely that of the animal in the previous protocol that it would be impossible to tell them apart. The same diminution in spontaneous movements, loss of sense of position, hypotonia, and active deep reflexes were present in the same degree.

June 29, 1933: Twelve days after operation.—The animal's behaviour has taken the same course as that of the previous animal. The symptoms are confined to the hind limbs and consist of inability to use the limbs accurately for grasping, hypotonia, assumption of abnormalities of posture, with retention of deep reflexes and of pain and tactile sensibilities.

This animal showed the same degree of disability in the hind limbs as did the animal with the lesion in the lower third of the thoracic region. The integrity of four or five thoracic segments had no influence on the symptoms.

Anatomical Study.

The cord was studied with the Marchi method. The lesion was seen to section the dorsal columns and to be confined to these. The degeneration could be easily followed to the nucleus of Goll in the medulla.

These four protocols demonstrate the essential features of lesions in the dorsal columns. Other lesions, or combinations of such lesions, were produced, including section of the column of Goll in the cervical region, section of part of the dorsal column in the thoracic region, hemisection of the dorsal columns, &c., but the essential features of the lesions and of their effects have been illustrated sufficiently by the four protocols presented.

IV.—DISCUSSION.

In general we may say that the uniformly characteristic symptoms presented by our animals with lesions of the dorsal columns were: (1) loss or diminution of the sense of position or of movement, or of both, in the limbs involved; (2) loss or diminution of active spontaneous grasping in these limbs; (3) hypotonia; (4) retention or even increase of the deep reflexes; and (5) loss or diminution of the placing and hopping reflexes in the limbs involved. This complex symptomatology appears to be mainly dependent upon involvement of the sense of position or perhaps of movement, or at any rate of a sense which enables the animal to appreciate postures of the limbs and continuity of movement. Especially in cases where the impulses from the upper extremity are involved, the animal does not appear to be able to accomplish successfully, or even to initiate, the finer types of spontaneous movement, such as grasping. On the other hand, there is no definite paralysis. Further evidence in favour of the origin of the symptoms from lesions of the dorsal columns comes from other animals in which we have recorded similar findings following lesions of the postcentral convolutions, or of the dorsal column nuclei in the medulla.

We have not described the animals as having ataxia after the operations, because we feel that from the physiological standpoint it is better merely to describe what an animal can or cannot do rather than to label it with a word which merely means "a lack of order," and connotes some hypothesis as to its origin. Clinically we speak of "spinal" or "cerebellar" ataxia, according to whether the disorder is associated with a lesion to the dorsal columns or with a lesion of the cerebellar system. This

differentiation is not entirely justified in our observations. We conclude from our anatomical work that the dorsal columns in the cervical region carry an important cerebellar component as well as the deep conscious components of sensibility from the upper extremities. Thus a lesion in the dorsal columns in this region produces an ataxia due in part to involvement of cerebellar components as well as of strictly dorsal column or sensory components. The sharp differentiation into two types of ataxia would not, therefore, be justified in these cases. On the other hand, when the lesion of the dorsal columns is confined to the lower cord, where the dorsal columns component to the cerebellum is not present, the incoördination may more properly be spoken of as a "spinal ataxia" in the usual sense of the term, the cerebellar ataxia developing only if there be an additional involvement of the cerebellar pathways in the lateral columns.

Space does not permit here of a discussion as to the relationship of sensory defects of various types to abnormal movements. As stated above the fundamental defects in the motor behaviour of our monkeys, particularly in those with lesions in the dorso-lumbar region, seemed to be due to some defect of deep sensibility.

The more superficial forms of sensation, such as pain and diffuse touch, seemed to be intact after the operations. However, our methods of testing for these were very gross and it is possible that quantitative defects occurred in these forms of sensation not revealed by our experimental technique. It has been mentioned that pinching of the dorsal columns is associated with a painful sensation. Many of our monkeys jumped violently at the moment when the lesion was produced in the dorsal columns even though they were under deep anæsthesia. As stated before, Kroll found a definite diminution in the skin pain spots below the level of the lesion when he sectioned the dorsal columns in the human subject. It is possible, therefore, that owing to a diffuse distribution of pain tracts only a slight loss of pain sensibility would result from lesions of the dorsal columns, and that a large lesion of the spinothalamic tract would be necessary to produce any gross defect of pain such as might be detected in the monkey.

One of the most interesting clinical features in the monkeys was the inequality already mentioned in the intensities of the symptoms in the front and hind limbs resulting from cervical lesions. When the cervical dorsal columns were completely sectioned at a level above that of the zones of entrance of all sensory roots from the fore limbs, for example, at the third or fourth cervical segment, the involvement of the fore

limbs was immeasurably greater than that of the hind limbs, the fore limbs being practically useless at a time when the animal had already learned to jump fairly well on its hind limbs. Then again, when lesions were made in the columns of Burdach alone at similar levels, the involvement of the fore limbs was always much more severe than was the involvement of the hind limbs in cases where the columns of Goll were sectioned above the levels of entry of the sensory roots from the lower limbs.

Bechterew noted severer disturbances in the fore limbs in the dog following cervical dorsal column lesions and attributed this to the short course in the cord of fibres of the dorsal column associated with deep sensations, many fibres from the hind limbs leaving them before reaching cervical levels. With this exception we have been unable to find in the literature any mention of this inequality in intensity of the symptoms between front and hind limbs, and therefore no attempt has been made to formulate any concept as to the functional differences between the posterior columns at high cervical or low thoracic levels. We believe that we can offer an explanation for the differences observed. From anatomical and experimental work which we are reporting elsewhere [24, 25], we have been able to confirm the existence of three main cellular groups in the terminal dorsal column nuclei in the medulla. The first two groups are the well-recognized nuclei of Goll and Burdach proper, which receive the fibres from the columns of Goll and Burdach and send their axons in the main into the medial lemniscus. The third large group of cells has been variously described as the nucleus of Monakow, the nucleus corporis restiforme, the nucleus of Blumenau, the external cuneate nucleus, &c. We prefer to call it the nucleus of Clarke-Monakow, in favour of Clarke who first described it, and Monakow who first established its cerebellar connections. We have been able with four series of experiments to confirm Monakow's view as to its cerebellar connections. We have been unable to determine its afferent spinal connections in the monkey. We have also been able to delimit anatomically the three main groups of cells, and finally we have established the very important direct connections of the nucleus of Clarke-Monakow with the dorsal roots of the cervical and upper dorsal segments of the spinal cord. These connections are established directly through the column of Burdach which sends a large portion of its fibres to the nucleus of Clarke-Monakow in addition to those which terminate in the nucleus of Burdach.

We have thus established that the columns of Burdach carry in addition to the long sensory afferent fibres a large cerebellar component.

of afferent fibres from the upper extremities. On the other hand, this cerebellar component from the hind limbs is carried outside of the dorsal columns. A lesion of the dorsal columns in the cervical region will thus interrupt two large and important groups of fibres from the upper limbs, namely, that passing to the nuclei of Goll and Burdach and connected with the medial lemniscus, and that going to the nucleus of Clarke-Monakow and then to the cerebellum. The addition of the cerebellar component in the lesion at this level is not met with in dorsal column lesions in the low dorsal, lumbar or sacral regions, where the cerebellar component travels in the main in the spino-cerebellar tracts. Therefore it may be easily seen that due to the loss of two main afferent components from the upper limbs cervical lesions would be associated with a greater involvement of such upper limbs as compared with the lower limbs.

It is of interest to note here that Bechterew described loss of equilibrium as one of his most constant findings in dorsal column lesions. He attributed this to section of fibres which he believed to pass through the dorsal columns and their nuclei directly into the cerebellum. Although Bechterew was right in attributing some cerebellar component to the cervical dorsal column, the direct cerebellar pathway from the posterior column to the cerebellum, which he used as the anatomical substratum for his explanation, still remains a doubtful one. Many writers have denied its existence. Even the various other connections between the nuclei of Goll and Burdach and the cerebellum such as the internal, external and posterior arcuate fibres, still retain a controversial status. This is due probably to the absence of absolutely reliable serial sections of brains with localized lesions in the terminal nuclei of Goll and Burdach.

SUMMARY.

(1) As a result of experimental lesions of the posterior columns in *Macacus rhesus* monkeys characteristic symptoms follow, represented mainly by loss or diminution of sense of position and loss or diminution in the ability for spontaneous fine grasping in the limbs involved. There is in addition hypotonus associated with retention, and at times increase, of the deep reflexes and loss or diminution of the placing and hopping reflexes.

(2) The symptomatology following lesions of the posterior columns in the cervical cord above the zone of entrance of the posterior roots for the fore limbs is much more severe in the fore limbs than is the disturbance in the hind limbs following lesions of the posterior

columns in the dorsal or lumbar region above the zone of entrance of the posterior roots for the hind extremities.

(3) The difference in symptomatology is explained by the fact that in the posterior column of the sacral, lumbar and dorsal segments there are only afferent sensory fibres. In the posterior column of the cervical segment, there are also afferent fibres to the cerebellum.

(4) It follows that while the symptomatology resulting from section of the dorsal columns in the dorso-lumbar and sacral region is the expression of what might be termed spinal ataxia, the symptoms following lesions of the posterior column in the cervical region is the expression of both spinal and cerebellar ataxia.

(5) The anatomical pathway carrying proprioceptive impulses to the cerebellum in the posterior column is represented by numbers of fibres which end in the so-called nucleus of Clarke-Monakow from the column of Burdach. The axons of this latter nucleus then enter the cerebellum via the corpus restiforme.

(6) In the cervical segments the posterior columns contain, in addition to the long system of fibres, an important cerebellar component represented by fibres running to the terminal nucleus of Clarke-Monakow. The fibres originating from this nucleus may be considered analogous to the fibres originating from Clarke's columns in the dorso-lumbar segments.

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INORGANIC CONSTITUENTS OF CEREBROSPINAL FLUID v. VENTRICULAR AND LOCULATED FLUID.

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THE cerebrospinal fluid is still regarded by many as being formed by ultrafiltration through a non-specific membrane at the choroid plexus. It has been shown, however, in the previous papers of this series (McCance and Watchorn, 1931 and 1932, Watchorn and McCance, 1932 and 1933) that the amount of potassium and of magnesium found in human lumbar puncture fluids cannot be accounted for by ultrafiltration from serum. This was also found to be true of calcium when the serum calcium was very low, and Herbert (1933) has more recently shown that, when the serum calcium is abnormally high or low, ultrafiltration will not explain the amount of calcium found in lumbar puncture fluid. These results may be criticized on the grounds that the fluids analysed had been so changed in their passage from the ventricle to the lumbar region that they no longer represented the true serum ultrafiltrate which had first been formed. It was felt therefore that this possible criticism should be met by a study of these ions in fluids taken from various levels of the cerebrospinal system.

SOURCES OF MATERIAL AND METHODS.

The ventricular and other fluids were almost all from cases of cerebral or spinal tumours which were being operated upon or investigated in some way. The fluids in Table II were all taken under gas and oxygen anaesthesia. The ventricular and lumbar puncture fluids of each case in Table II and the cisternal and lumbar puncture fluids in Table III were taken within a few minutes of each other. Some of the material was obtained from the National Hospital for Nervous Diseases, Queen Square, but the greater part from King's College Hospital. The general technique including the analytical methods has been described in previous papers of this series.

RESULTS.

Table I shows the amounts of potassium, calcium and magnesium which have been found in ventricular fluids. Average values of serum, serum-ultrafiltrates and lumbar puncture fluid from previous papers of the writers have been added for comparison. It will be noticed that the concentrations of the individual ions in the ventricular fluids are close to those of the lumbar fluids and if anything are less like serum ultrafiltrates than are the lumbar fluids. If this is true, then there is a tendency for the fluid to come into equilibrium with the serum during the passage down the canal.

TABLE I.—VENTRICULAR FLUIDS.
(All figures represent milligrams per 100 c.c. fluid.)

	Potassium	Calcium	Magnesium
	11.60		
	9.16	7.16	3.44
	10.70	5.78	3.87
	8.80	5.00	3.60
	10.10	4.90	3.44
	12.90		3.26
		5.98	4.19
	12.81		3.44
			3.88
	11.14	5.39	3.79
		6.70	3.58
			3.81
		6.43	4.22
		5.61	4.34
	9.36	5.11	3.59
	10.42		
	10.13		
	10.34		
	11.45	5.29	3.61
	9.15	5.59	3.29
	11.57	5.49	3.01
Average	10.60	5.95	3.66
Average serum value ..	19.70	10.38	2.71
Average ultrafiltrate value	21.20	5.54	2.01
Average spinal fluid value	12.05	5.83	3.22

Table II shows a further series in which comparisons of the ventricular and lumbar fluids have been made on the same case. The results for magnesium and potassium corroborate in every respect those shown in Table I. The average amount of calcium found in the ventricular fluids is slightly below that in the lumbar fluid, whereas in Table I the reverse was the case. The differences are probably not significant.

TABLE II.—CEREBROSPINAL FLUID AND VENTRICULAR FLUID.

Calcium		Magnesium		Potassium		
Spinal fluid	Vent. fluid	Spinal fluid	Vent. fluid	Spinal fluid	Vent. fluid	
		8.42	8.74	7.96	8.11	
		3.89	3.62	7.38	7.31	
5.49	5.49	3.48	3.40	12.11	12.22	
5.48	4.31	2.49	2.59	12.21	10.00	
5.49	5.39	3.07	3.48	10.47	10.23	
6.08	5.98	3.06	3.25			
6.37	5.39	2.88	3.05			
		3.08	3.17			
Average ..	5.74	5.81	3.11	3.28	10.08	9.57

Since the fluid withdrawn from below a spinal tumour may differ very greatly in colour, protein content, &c., from normal cerebrospinal fluid, it was felt that an examination of these loculated fluids should be made.

Table III (Cases 1 to 8) shows the results which have been obtained. In Case 9 the lumbar fluid was withdrawn from just above the tumour. It will be noted that the amounts of magnesium and potassium resemble those in normal cerebrospinal fluids and not those in serum ultrafiltrates. When both cisternal and lumbar fluids were obtained

TABLE III.—LOCULATED FLUIDS.

Case No.	Calcium Mg./100 c.c.		Magnesium Mg./100 c.c.		Potassium Mg./100 c.c.	Protein grams/100 c.c.
	Serum	C.S.F.	Serum	C.S.F.	C.S.F.	C.S.F.
1	10.41 _x	6.76 _y	2.54 _x	3.85 _y		2.7
	9.12 _x		2.51 _x			
2	10.10	6.98	2.72	3.90		1.8
3				3.38	8.40	
4	11.91	5.98	3.21	3.45		
5		6.90		3.62		
6	10.45	6.90	2.91	3.85		0.5
7	11.42	8.06	2.80	3.38		6.4
8	11.32	7.14	2.46	3.54		1.0
		5.91 _a		3.54 _a		0.02 _a
9	9.90	5.78 _b	2.88	3.42 _b	11.01 _b	1.0 _b
		5.10 _a		3.72 _a	12.66 _a	0.04 _a
Average (omitting 8a, 9a and b)	10.45	7.2	2.75	3.55	3.4	
Average of previous figs for sera and spinal fluids	10.83	5.88	2.71	3.22	12.05	
Average ultrafiltrate ..		5.54		2.01	21.2	

x, y and z = Taken on successive days.

a = Cisternal fluid.

b = Fluid withdrawn from immediately above the tumour.

(Cases 8 and 9) the differences in protein content and the agreement in magnesium values are very striking. In most of the cases manometric measurements made at the time the fluid was withdrawn indicated a complete obstruction of the canal at the site of the tumour. This may not strictly have been the case, for fluid may have been able to percolate slowly past the tumour. One would have expected, however, that in loculated fluids, if anywhere in the cerebrospinal system, the concentrations of ions would have approximated to those of ultrafiltrates. That they show no tendency to do so suggests that the membranes lining the whole of the cerebrospinal spaces are of a specific character and similar to those of the choroid plexus.

DISCUSSION.

These results enable one to say with confidence that the magnesium and potassium in ventricular fluids cannot be accounted for by ultrafiltration from serum. Since the serum calcium throughout the present series was never grossly abnormal, and since the amount of calcium in the lumbar or ventricular fluid in such cases agrees approximately with that in an ultrafiltrate, it is not possible to be so dogmatic about this particular ion. It is probable, however, that could the ventricular fluids of cases with grossly abnormal serum calcium values be examined, they would be found, like the lumbar fluids, not to follow the serum fluctuations, for there is good reason to suppose that the fluid of the cerebrospinal system has usually the same ionic pattern from whatever source it is withdrawn.

With regard to the loculated fluids, these differ from normal cerebrospinal fluids in two respects: (1) They contain, as is well known, large amounts of protein; (2) they contain, as was pointed out by Critchley and O'Flynn (1924), more calcium (average 7.2 against 5.33 for non-loculated cerebrospinal fluid). One cannot regard these fluids as serum ultrafiltrates since the concentrations of magnesium and potassium are so unlike those of ultrafiltrates. The suggestion has often been made that the protein is derived not from the serum but from the tumour. Our results are in favour of this, since the concentration of magnesium and potassium resemble those of normal cerebrospinal fluid, which one would not expect if such large amounts of protein were leaking through from the blood-vessels. It is possible that the study of other electrolytes now being undertaken may help to supply further evidence. The excess of calcium is probably associated with the increased protein but there is no sound evidence at present as to its source.

SUMMARY.

(1) Ultrafiltration will not explain the amounts of potassium and magnesium found in ventricular fluids. Such fluids in fact appear to contain slightly more magnesium and less potassium than lumbar fluid. As regards these two ions, therefore, ventricular fluid is even less like a serum ultrafiltrate or a pathological transudate than is the spinal fluid.

(2) Judged by their magnesium and potassium contents, loculated fluids taken from below spinal tumours resemble ventricular fluids or spinal fluids and not serum ultrafiltrates. Such loculated fluids appear to contain more calcium than fluids from the ventricles, normal cerebrospinal fluid or serum ultrafiltrates, and this may be connected with their large protein contents.

The authors are greatly indebted to a number of people who have assisted them to obtain the material for this investigation and helped in other ways, especially to Mr. C. P. G. Wakeley, Dr. J. G. Greenfield, and Dr. E. A. Carmichael. One of us (Miss E. Watchorn) has carried out the work during the tenure of a personal grant from the Medical Research Council.

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THE RELATIONSHIP BETWEEN THE SUGAR AND UREA CONTENTS OF THE BLOOD AND CEREBROSPINAL FLUID.

BY J. N. CUMINGS AND E. ARNOLD CARMICHAEL.

(Work undertaken on behalf of the Medical Research Council at the Neurological Research Unit and Pathological Laboratory, National Hospital, Queen Square, London.)

CONSIDERABLE diversity of opinion prevails as to the relationship between the sugar content of the blood and that of the cerebrospinal fluid. There is also a paucity of records dealing with the comparative urea content of the blood and of the cerebrospinal fluid. In this paper is described a series of investigations undertaken to further our knowledge regarding these relationships in comparatively healthy subjects.

Fremont-Smith and Dailey (1925) were able to demonstrate in three subjects that following a glucose meal the lumbar fluid sugar rose by not more than 6 mgm. while that of the blood rose and fell as in a normal blood-sugar curve. In one subject, the blood sugar was rapidly raised to 290 mgm. per cent. after intravenous glucose; during the ninety minutes following the injection, a rise of 9 mgm. occurred in the fluid sugar. Riser (1929) gives the figures from one case in which he found that the fluid sugar was raised by 3 mgm. following the ingestion of glucose. Findings comparable to the above are also reported by Wittgenstein (1923). In contrast to the above observations, other authors have demonstrated that there is a parallelism between the blood and fluid sugar levels (Schloss and Schroeder (1916), Polonowski and Duhot (1923)). Jacobsen (1932) and Münch-Petersen (1930) record a slight rise after a glucose meal in the lumbar fluid sugar with a greater rise in the cisternal fluid sugar in a series of subjects suffering from epilepsy. With these observations Schjott (1931) agrees, but emphasizes the fact that this disparity occurs more frequently in epileptic than in other subjects. Chevassut (1927) appears to be the only English author to investigate these relationships; she concludes, after examination of single specimens of ventricular fluid and of blood, that the ventricular fluid sugar and that of the blood are identical in the same individual at the same time. The lumbar and ventricular fluid sugars have also been compared by Fremont-Smith and Dailey (1925), Riser

and Merrill (1927), Cestan, Riser and Laborde (1923). Apart from two of the cases reported by Riser and Merrill, the ventricular fluid sugar level has been invariably higher than that of the lumbar fluid. Riser (1929), however, expresses the opinion, as the result of the examination of many fluids, that the sugar in the fluids from these different sites is in equal concentration at any same point of time.

The relationship of fluid urea to blood urea, as determined by an examination of single specimens, has been investigated by Merritt and Fremont-Smith (1934), Cestan, Riser and Laborde (1923), and Levinson (1929), who are of opinion that the lumbar fluid urea content is similar to that of the blood.

EXPERIMENTAL PROCEDURE AND RESULTS.

(a) *Sugar*.—A series of young adults admitted for non-organic conditions of the nervous system and not suffering from epilepsy were investigated in order to determine the blood and lumbar fluid sugar levels following the ingestion of a known quantity of glucose (50 grm.) after a night's fast. In five, specimens of lumbar fluid were obtained before the giving of glucose and at varying intervals during the period of two hours immediately following. Specimens of blood from the ear were taken simultaneously with the collection of the fluid specimens. During these procedures the subject lay quietly in the horizontal position with the lumbar needle in situ. Similar investigations in four other cases were undertaken; in two, the lumbar fluid was withdrawn at intervals during the period between one and a half to three and a half hours, and in the other two during the period between three and five hours after the glucose meal. From all four subjects, specimens of blood were obtained before the giving of glucose and during the whole three and a half and five hour periods. In another series of seven cases, isolated samples of blood and ventricular fluid were taken simultaneously at varying intervals; in two of these subjects it was possible to obtain samples on different days. All the subjects from whom ventricular fluid was obtained presented symptoms referable to the presence of intracranial tumour.

In one case with considerably increased intracranial pressure, specimens of blood and ventricular fluid were obtained at intervals over a period of two hours. In another case without increased intracranial pressure, it was possible to obtain samples of blood and ventricular

fluid, under fasting conditions and for one and three-quarter hours after a glucose meal.

The chemical estimations for sugar were performed immediately by the method of Hagedorn and Jensen. Two estimations were performed

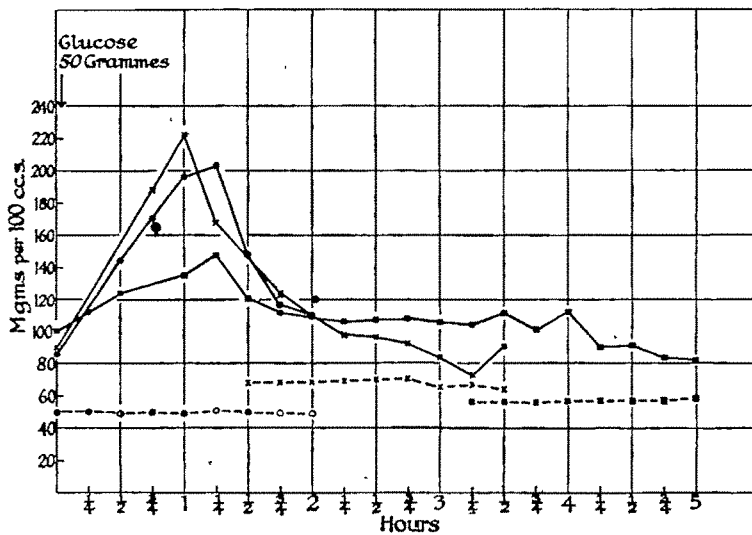


Fig. 1.—The blood sugars are represented by continuous lines and the fluid sugars by interrupted lines.

on each specimen of fluid; the difference between the results of each pair was never greater than could be explained by the limitations of the method. The figures quoted are the mean of the two.

TABLE.

Name	Date	Amount in gram. of glucose given	Time in minutes specimens were taken after glucose meal	Blood sugar in mgm. per cent.	Ventricular fluid sugar in mgm. per cent.
Mr. G. . .	2.6.34	50	45	156	82.5
	4.6.34	50	25	146	88
	6.6.34	Nil	—	129	90.5
Mrs. M. . .	7.6.34	50	25	167	58.5
	15.6.34	50	10	114	68
Mr. E. . .	15.6.34	50	35	188	57
Mrs. A. . .	19.6.34	Nil	—	188	82.5
Mr. L. . .	28.6.34	50	70	120	82.5
Mr. X. . .	6.7.34	25	80	191	64
Mr. A. . .	17.8.34	50	65	74	56

An analysis of the results, in the nine investigations dealing with the lumbar fluid, showed no rise in the sugar content of the fluid up to a period of five hours after the glucose meal. Fig. 1 shows typical findings in the blood and fluid from three cases from which specimens were obtained over a period of five hours.

In the series of cases in which the sugar content in isolated samples of blood and ventricular fluid were estimated, the ventricular fluid sugar has been found to be invariably lower than that of the blood. It was impossible in these cases to obtain a blood sugar curve so that no statement can be made as to whether the blood sugar was rising or falling.

In the subject showing no evidence of increased intracranial pressure and in which a ventricular fluid sugar curve was obtained, the

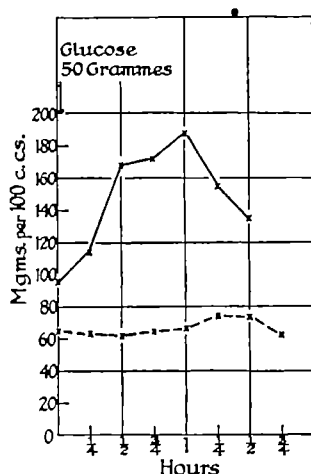


FIG. 2.—The blood sugar is represented by a continuous line and the fluid sugar by an interrupted line.

blood sugar rose and fell as in a normal individual; at the end of seventy-five minutes after the giving of glucose the ventricular fluid sugar content had risen by 9 mgm. when the blood sugar was falling. Thirty minutes later the ventricular fluid sugar had fallen to 2 mgm. below the fasting level (*see* fig. 2). During this investigation there was a continuous small loss from the ventricular needle of 6 c.c. of fluid per hour; this loss may have some bearing on the slight rise in the ventricular fluid sugar level.

The other ventricular fluid sugar curve was from a subject with

increased intracranial pressure. In this case the blood sugar curve was of a mild diabetic type and was still rising at the end of two hours after the ingestion of glucose; the ventricular fluid sugar continuously rose to a lower level.

(b) *Urea*.—After a night's fast, a known quantity of urea (30 grm.) was given by mouth to six cases. Specimens of blood and lumbar fluid were taken at identical times before and at frequent intervals following the administration of the urea. In the first two cases, lumbar fluid was obtained immediately before and for two hours following the administration of urea; in the next two cases, the lumbar fluid was withdrawn during the period of two hours commencing one and a half hours after the giving of urea; in the remaining two cases, the lumbar fluid was taken during the period from the third to the fifth hour after the urea meal. In all six cases, frequent estimations of the blood urea were carried out from immediately before the administration of the urea until the withdrawal of the last sample of cerebrospinal fluid.

While it is impossible to keep the blood sugar level constantly rising, it is possible to do this to the blood urea level by the repeated administration of doses of urea by mouth. This method of approach to the problem appeared worthy of trial and six subjects were submitted to the procedure. In two, urea was given twice during a period of three and a half hours and in another thrice within five hours. Each dose of urea was of 30 grm. and was given at about one and a half hourly intervals. In each case, blood urea estimations were frequently made and, once it was found that the blood urea level was high, lumbar puncture was performed and specimens of fluid were taken for the subsequent two hours. In three other cases intensive feeding with urea made it possible to raise the blood urea to an even higher level. In the first of these, 130 grm. of urea in eight doses were given over a period of eight hours, during the last two of which the lumbar needle was in situ. In the second, 155 grm. of urea were given in eight doses during eight hours and specimens of the lumbar fluid were withdrawn during the last one and a half hours; in the last experiment with a duration of ten hours, during the last two of which specimens of lumbar fluid were obtained, 165 grm. of urea were given in ten doses. In all three experiments the blood was sampled frequently and the urea content estimated.

The estimations for urea were performed immediately on the blood and fluid samples by Archer's modification of the method of Folin and Wu. Duplicate specimens of the fluid were estimated in every instance

and the percentage of error was less than that obtained in the sugar estimations.

The six experiments in which a single dose of urea was administered gave results indicating that no rise occurred in the lumbar fluid urea content, either synchronous with or after the rise of blood urea. Fig. 3 gives lumbar fluid and blood urea curves illustrative of these results.

In two subjects, to whom two doses of urea had been given, the blood urea rose from 30 to 124 mgm. per cent., and from 36 to 170 mgm. per cent. respectively. In the former subject, the lumbar fluid urea rose from 28 to 40 mgm. per cent. and was the same in the last two estimations; in the latter subject there was a rise of 4 mgm. in the lumbar fluid over a period of one and three-quarter hours. In the subject given three doses of urea, the fasting blood urea was 50 mgm.

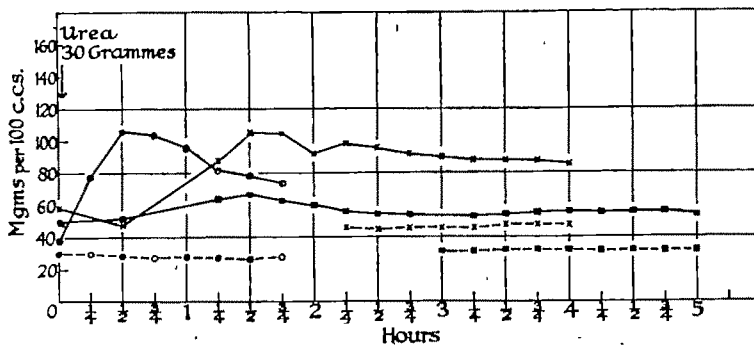


FIG. 3.—The blood ureas are represented by continuous lines and the fluid ureas by interrupted lines.

per cent. and at the end of three and a quarter hours the lumbar fluid urea was found to be 70 mgm. per cent., when the blood urea had risen to 164 mgm. per cent. During the next three-quarters of an hour the blood urea continued to rise to the high level of 234 mgm. per cent. The blood urea slowly fell during the next hour to 194 mgm. per cent., while the lumbar fluid urea rose to 85 mgm. per cent. and remained at that level for the last two estimations.

In the first of the experiments in which intensive feeding over a period of eight hours was practised, the fasting blood urea was 50 mgm. per cent.; this had risen at the end of six hours to 142 mgm. per cent., and thereafter for the next two hours rose steadily, eventually to reach

the level of 178 mgm. per cent. At the end of the sixth hour the lumbar fluid level was 50 mgm. per cent. This corresponded to the fasting blood urea level and as the blood and fluid fasting levels are accepted as being identical it may be assumed that no rise in the lumbar fluid level had occurred by the end of the sixth hour. During the next three-quarters of an hour the fluid urea remained constant, to rise 8 mgm. during the next half-hour and thereafter to remain at this level of 58 mgm. per cent. In the second case, the fasting blood urea was 37 mgm. per cent.; this had risen to 192 mgm. per cent. at the end of six and a quarter hours, after which a fall to 153 mgm. per cent. at the end of the experiment had occurred. The first specimen of lumbar fluid obtained at six and a quarter hours after the commencement of the experiment contained 74 mgm. per cent. of urea; as this is above the fasting blood level it is indicative that a rise in the fluid urea content had taken place at an earlier time. During the next one and a half hours there was a fall of 9 mgm. in the fluid urea content. In the last experiment of intensive and prolonged feeding with urea, the fasting blood urea was 58 mgm. per cent.; at the end of nine and three-quarter hours it had risen to 280 mgm. per cent. Lumbar fluid taken at eight hours contained 80 mgm. per cent., which concentration persisted till the termination of the experiment at ten hours. As the fluid urea was higher than the fasting blood urea, a rise in the fluid level had occurred during the first eight hours whilst the blood urea had been rising. Figures obtained in all experiments not quoted in detail or illustrated in the text will be found at the end of the paper.

DISCUSSION.

It has been shown that the levels of sugar and urea in the lumbar fluid remain constant following the ingestion of known quantities of glucose and urea. The amounts of glucose and urea administered in these investigations produced changes in the blood levels, changes which are comparable to those following the taking of an ordinary meal containing carbohydrate and protein. Consequently it is unlikely that a fluctuation occurs in the lumbar fluid sugar and urea contents in a healthy person during twenty-four hours. The presence, therefore, of a high lumbar fluid sugar or urea becomes of clinical significance. Further the investigations show that marked alterations in the blood urea may occur without any similar alteration in the lumbar fluid. Accordingly in a patient exhibiting an acute rise of the blood urea, a coincidental

and similar rise in the lumbar fluid level is not a necessary concomitant. Neither the sugar nor the urea contents of the lumbar fluid can be taken as indicative of the blood levels.

In the ventricular fluid it is possible to determine a small rise of the sugar content in association with a rise in blood sugar. As the rise recorded in the case without gross disturbance of intracranial pressure was so insignificant, and as during the experimental procedure there was a constant slight leak of ventricular fluid, it is probable, were it possible to examine ventricular fluid without removing any, that the ventricular fluid sugar in health would be found to remain constant in the presence of considerable fluctuation of the blood sugar. But when the blood sugar behaves in an abnormal way or when evidence of increased intracranial pressure is present, there is not infrequently found a rising sugar content or a relatively high one in the ventricular fluid. No figures are available to permit a statement as to whether the ventricular fluid urea in health rises as the result of a shift normally encountered in the blood urea. From the similarity of the results in the sugar and urea experiments, we are of the opinion that if any rise in the ventricular fluid urea does occur it will be minimal and of no clinical significance.

Do the results of these investigations support any one theory of the origin of the cerebrospinal fluid? When the above results are interpreted in the terms of the dialysate theory of the formation of the cerebrospinal fluid, difficulties are immediately encountered. On the basis of this theory, sugar and urea when increased in the blood should pass through to the cerebrospinal fluid and if the increase in the blood is continuous, a continuous alteration in the fluid should occur until a state of equilibrium is reached. The behaviour of the lumbar fluid sugar and urea as determined in these investigations does not conform to this theory. It is possible that a slow rate of diffusion of these two substances in the cerebrospinal fluid might account for the failure to detect evidence indicating that the lumbar fluid contents approached those of the blood; in other words the time factor may not have been sufficiently investigated. This is improbable as the experiments covered a period of five hours, by which time the blood contents had returned to normal. More important are the observations of the behaviour of the ventricular sugar content after a glucose meal and of the lumbar fluid urea following intensive feeding with urea. In the ventricular fluid it has been demonstrated that, when the pressure is normal, there is no significant rise of the ventricular sugar coincident with that of the blood. It may be suggested that the area of surface,

namely the choroid plexus, through which dialysis can take place, is very small and that the apparently insignificant changes observed in the ventricular fluid are in fact evidence of dialysis; and in support of this could be quoted the observations demonstrating a rise in ventricular-fluid sugar when the blood sugar was abnormal and continued to rise. But the results obtained with intensive urea feeding are of great importance. Urea being more rapidly diffusible than sugar, it is to be expected that the urea content in the lumbar fluid would continue to rise as long as a rise in the blood urea continues to take place. In fact no rise in the lumbar fluid urea occurs in association with the rise in the blood urea when the urea administered is similar in quantity to that obtained from ordinary diets. When intensive feeding of urea is resorted to, the blood urea can be made to rise to a very high level over a period of hours; during the same period the lumbar fluid urea rises only a small amount and may then cease to rise even though the blood urea continues to increase. This finding indicates that the fluid urea does not follow the laws of dialysis. It is apparent, therefore, that the choroid plexus must play an active part in controlling the level of fluid urea and that the choroid plexus does not act simply as a dialysing membrane.

To determine the nature of the functional activity of the choroid plexus by a comparative study of the blood and fluid contents in diabetes and uræmia is open to the criticism that the choroid plexus may be damaged by the disease process. There is histological evidence that in uræmia the cells of the choroid plexus are abnormal. It is impossible to explain by the theory of dialysis the presence in the fluid of a urea content higher than that in the blood. Recently an opportunity was afforded us, in a case of uræmia, to make repeated observations over a period of twenty-four hours on the blood and lumbar fluid urea levels. When first examined the blood urea was 340 mgm. per cent. and the lumbar fluid urea 332 mgm. per cent.; sixteen hours later the blood urea was 523 mgm. per cent., the fluid urea 592 mgm. per cent., and at the last examination, seven hours later, the blood urea was 560 mgm. per cent. and the fluid urea 640 mgm. per cent. In the presence of a continuous rise of blood urea, the fluid urea originally at a lower level eventually rose to 80 mgm. above that of the final blood urea. No evidence was present that any profound change had occurred in the other chemical constituents of the blood; in the absence of such a change, the choroid plexus must have taken an active part in raising the fluid urea above that of the blood. These observations in a case of

uræmia, therefore, uphold our view based on the experiments recorded in this paper that the choroid plexus actively participates in the control of some of the contents of the cerebrospinal fluid and is not merely a passive dialysing membrane.

SUMMARY.

(a) A series of investigations are described which have been undertaken to determine the relationship between the sugar and urea contents of the blood and cerebrospinal fluid.

(b) It has been shown that the levels of sugar and urea in the lumbar fluid do not rise in association with a normal rise in the contents of these substances in the blood.

(c) Estimations of ventricular fluid sugar have been made. These demonstrate that only in abnormal conditions is there any rise in the fluid sugar in association with a rise in the blood sugar.

(d) The bearing these findings have upon the theory of the nature of the cerebrospinal fluid is briefly discussed. It is suggested that the findings are in favour of the choroid plexus taking an active part in the control of the level of sugar and urea in the cerebrospinal fluid.

It is with pleasure that we express our gratitude to the members of the staffs of the National and King's College Hospitals for permission to carry out these investigations upon patients under their care.

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SUGAR EXPERIMENTS.

(Time is expressed in hours, and sugar in milligrammes per cent. The glucose meal was given immediately after the first estimation.)

MR. K.

Time	Blood sugar	Lumbar fluid sugar
0.0	74	68
0.5	90	67
0.10	116	62
0.15	122	61
0.20	136	68
0.25	161	68
0.30	177	69
0.35	178	69
0.40	184	70
0.45	200	64
0.50	208	68
0.55	212	70
1.0	206	68
1.5	198	67
1.10	184	69
1.15	176	69
1.20	168	69
1.25	144	71
1.30	130	68

MR. O.

Time	Blood sugar	Lumbar fluid sugar
0.0	85	52
0.15	141	51
0.30	177	55
0.45	186	52
1.0	141	57
1.15	110	58
1.30	105	55
1.45	81	58
2.0	79	59

MR. MacR.

Time	Blood sugar	Lumbar fluid sugar
0.0	79	—
0.45	163	—
1.0	127	—
1.35	117	50
1.50	111	49
2.5	88	49
2.20	77	48
2.35	79	52
2.50	92	52
3.5	81	54
3.20	79	54
3.35	74	55

MR. B.

Time	Blood sugar	Lumbar fluid sugar
0.0	68	44
0.15	135	48
0.30	174	46
0.45	160	47
1.0	115	48
1.15	100	47
1.30	96	52
1.45	82	51

MR. E.

Time	Blood sugar	Lumbar fluid sugar
0.0	95	64
0.15	111	66
0.30	142	67
0.45	178	69
1.0	197	67
1.15	223	65
1.30	200	64
1.45	178	64

MR. H.

Time	Blood sugar	Lumbar fluid sugar
0.0	77	—
0.30	104	—
1.0	126	—
1.30	114	—
2.0	86	—
2.30	75	—
3.0	73	50
3.15	86	56
3.30	92	55
3.45	104	57
4.0	95	59
4.15	86	57
4.30	98	55
4.45	104	54
5.0	86	57

CASE WITH INCREASED INTRACRANIAL PRESSURE AND EXHIBITING A BLOOD SUGAR CURVE OF MILD DIABETIC TYPE.

MRS. F.

Time	Blood sugar	Ventricular fluid sugar
0.0	110	—
0.15	154	—
0.30	158	80
0.45	184	87
1.0	186	92
1.15	228	95
1.30	209	105
1.45	220	106
2.0	234	114

UREA EXPERIMENTS.

(Time is expressed in hours and urea in milligrams per cent. The urea meal was given immediately after the first estimation.)

MR. F.			MR. D.		
Time	Blood urea	Lumbar fluid urea	Time	Blood urea	Lumbar fluid urea
0.0	82.4	82.4	0.0	85.6	—
0.15	84.1	81.9	0.15	41.0	—
0.30	67.6	82.1	0.30	52.4	—
0.45	72.4	29.8	0.45	62.0	—
1.0	76.2	31.0	1.0	66.4	—
1.15	86.6	38.0	1.15	69.4	—
1.30	78.2	32.8	1.30	62.0	—
			1.45	62.6	—
			2.0	61.6	37.7
			2.15	61.4	37.4
			2.30	57.6	40.6
			2.45	53.4	38.8
			3.0	54.6	36.5
			3.15	—	38.0
			3.30	52.0	37.8
MR. J.					
0.0	30	—			
0.30	35	—			
1.0	36	—			
1.30	42	—			
1.45	58	—			
2.0	61	—			
2.15	54	—			
2.30	53	—			
2.45	56	—			
3.15	61	26.0			
3.30	53	26.3			
3.45	50	27.0			
4.0	52	24.8			
4.15	48	25.0			
4.30	45	25.5			
4.45	52	27.5			
5.0	46	27.0			

NOTICES OF RECENT PUBLICATIONS.

Nutrition and Disease: The Interaction of Clinical and Experimental Work. By E. MELLANBY: London and Edinburgh. Oliver and Boyd. 1934. Price 8s. 6d.

There is prevalent a dubiety as to the relative value of laboratory investigation and that performed at the bedside in the advancement of knowledge in medicine. The protagonists of either will do well to read this volume. Herein the author describes his personal experience gained in investigating nutritional problems, and in a lucid manner demonstrates the importance of a combination of laboratory and clinical research. Certainly the book is an able plea for more and better facilities for such combined work.

To neurologists the chapters dealing with the production of changes in the nervous system following alteration in diet are of great interest. The author demonstrates the close similarity of the experimentally produced lesions to those found in certain diseases afflicting man. The view expounded that the nervous manifestations of pellagra are closely linked to vitamin A deprivation is contrary to that usually expressed by the majority of workers on the subject. The resemblance of subacute combined degeneration of the cord to pellagra is commented upon, and the possible part played by vitamin deprivation in the former is discussed at length. Appreciating the importance of vitamins in preventing many maladies, the author suggests that the results of work in nutrition might with benefit be applied to an investigation of disseminated sclerosis. He quotes several clinical experiments of his own, but hesitates to be in any way dogmatic as to the interpretation of the results. Only work undertaken by two generations of workers will demonstrate satisfactorily the value of therapeutic measures to the disease.

The Sadleir Trust of the Royal College of Physicians is to be congratulated on making available in a form so clear and succinct the work and views of the author, a recognized leader in the study of nutrition.

The Principles and Practice of Neurology. By A. CANNON and E. T. HAYES. With a Special Clinical Examination by Professor G. H. Monrad-Krohn. London: W. Heinemann, Ltd. 1934. Price 25s.

Students of neurology seeking help in textbooks find at their disposal a number which is steadily being added to. It therefore behoves the student to discriminate with care as to which is best suited to his purpose, as often one textbook supplies some valuable information not readily available in another. In this present book, written "to present to the student and practitioner the

essentials in clinical examination, diagnosis and treatment of nervous diseases," the student will find much valuable advice and information regarding the method of clinical examination of the nervous system in the part written by Professor Monrad-Krohn. The second part, written by the authors, deals with diseases of the nervous system. Why injuries to the meninges should be included in the chapter on epidemic diseases, and hysteria in that on diseases of the spinal cord is difficult to understand. That tuberculomata are the most common spinal tumour is unlikely to receive confirmation from neurological centres. That polycythæmia vera should receive as much space as is devoted to a description of lesions of the cauda equina and conus medullaris tends to make the book an ill-balanced one, and further, a textbook, not of neurology alone, but of diseases not usually accepted as primarily affecting the nervous system.

It is to be hoped that the authors, should they publish a second edition, will see their way to revise many of their statements and the method of presentation.

A Textbook of Medical Psychology. By E. KRETSCHMER. Translated, with Introduction, by E. B. STRAUSS. London: Humphrey Milford, Oxford University Press. 1934. Pp. 274. Price 15s.

Dr. Strauss has rendered a service to English readers in translating this well-known work, of which the German edition has been reviewed here earlier. So frequently is the Freudian or related theory assumed to be the only medical psychology, that it is of especial importance to have in this accessible form a concise presentation of the wider psychopathology which is based on a knowledge of the whole range and treatment of mental disorder as well as of psychology in its various aspects. The book is, of course, an exposition of German teaching, not always in conformity with that prevalent in England; the author's own interest and studies receive perhaps disproportionate notice. But there is no complete work in this field, and a conspectus by so active and eminent a worker as Professor Kretschmer cannot fail to be valuable. The translation is painstaking and clear.

Psychology and Psychotherapy. By WILLIAM BROWN. Third Edition. London: Edwin Arnold. 1934. Pp. 252. Price 12s. 6d.

This work might reasonably be regarded as an authoritative exposition of medical psychology in view of the author's academic position and the experience and success in therapy of which the book makes frequent mention. If this be so, it constitutes a severe criticism of the scientific claims of medical psychology. There is here no coherent theory or doctrine, but much vague speculation and appeal to superficially recorded personal experience; also expressions of conviction without evidence and unwarranted assurances that this or that is "obvious." To scientific requirements of proof less regard is paid than in comparable works in other branches of medicine and psychology. These

strictures do not apply to the short mathematical appendices which appear, however, to have hardly any connection with the rest of the book. The author's point of view is professedly synthetic as regards the differing schools of medical psychology, but actually he states what might have been thought rather advanced views twenty years ago. Of modern developments there is only superficial mention and none at all of psychopathology in the wider sense and its relations to psychiatry. The fourteen chapters of the book (which are mainly revised articles from various medical and lay journals) deal in part with clinical topics such as the psychoneuroses of war and the treatment of alcoholism, in part with the older Freudian theories, hypnotism and such philosophic problems as the mind-brain relation and the Eternal Values. The treatment of the main matter is not adequate or profound, though often adroit, smooth and even casually impressive.

Mental Defect. By LIONEL S. PENROSE. London: Sidgwick and Jackson: 1933. Pp. 183. Price 8s. 6d.

This book is published as one of a series of textbooks of Social Biology, and though by no means a textbook, it takes more account of the biological aspect of mental defect than has been the custom in earlier English works. Its main concern is the relative significance of hereditary and environmental factors in the causation of this disorder; such other material as is included is only complementary. The author is clearly better equipped to deal with these aspects of his problem than with the more clinical and pathological ones; the physical changes that may accompany defect and the psychiatric problems are skimmed over and sometimes mis-stated. The statistical treatment is better than that usually found in medical works, but shows evidence of a lack of statistical training, as in the blunder in the use of correlations on page 83. The choice of articles for footnote reference, though arbitrary, may be regarded as adequate for such a brief survey as this of the genetic and related aspects of defect. As a whole the book is interesting and does service by insisting on an essential method of study which had been neglected until the last few years.

Das Persönliche Tempo. Eine erbbiologische Untersuchung. von IDA FRISCHEISEN-KOHLER. Leipzig: Thieme. 1933. S. 63. Price M. 5.50.

Studies of constitution and inheritance now play a considerable part in psychological research. In the experiments reported in this monograph the individual tempo was measured by finding the rate at which subjects spontaneously tapped with hand or foot, or that which they found most agreeable on the metronome. By these and other less measurable procedures, the authoress examined the variations in the individual himself from time to time, between him and other members of his family and between twins. The individual tempo was found to be surprisingly constant in the same subject.

The variability of tempo between uniovular twins was the same as that for a single person; for binovular twins, as for ordinary siblings, it was twice as great; hence it is concluded that hereditary influences are at least 50 per cent. responsible for the manifestation of personal tempo. The variability is still higher between persons who are not related by blood to one another. A significantly high percentage of children have the same tempo as one or both of their parents. The mode of transmission of this inherited predisposition is left in doubt. The character, however, is not so readily investigated as to its Mendelian relations as the writer assumes; there are much the same difficulties as obtain when the inheritance of intelligence is being examined. Within its limits the monograph provides useful data on constitutional attributes.

Psychiatrische Vorlesungen für Aerzte. von Kurt Schneider. Leipzig : Thieme. 1934. S. 140. Price M. 3.40.

These articles, reprinted from a German medical weekly, give a straightforward presentation of clinical psychiatry, paying particular regard to the milder or earlier forms and those symptomatic of bodily affections. The author's earlier study of psychopathic personality and related problems ensures a well-informed account, in which the actual data are presented clearly without the interpolation of needless conjectures and technical terms. It is, however, not only clear but very brief and simple and suitable rather for the medical student than for the psychiatrist.

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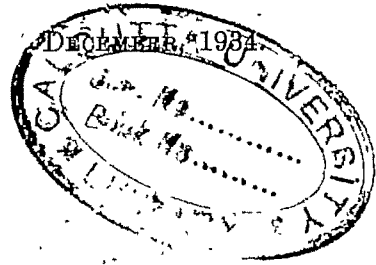
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BRAIN.

PART 4, VOL. 57.

THE BERGER RHYTHM: POTENTIAL CHANGES FROM THE OCCIPITAL LOBES IN MAN.

BY E. D. ADRIAN AND B. H. C. MATTHEWS.

(*from the Physiological Laboratory, Cambridge.*)

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INTRODUCTION.

DURING the past five years Hans Berger (1929-1933) has published a series of papers dealing with a remarkable electric effect which can be detected in the human subject by electrodes applied to the head. It consists of a rhythmic oscillation of potential with a frequency in the neighbourhood of 10 a second, appearing when the subject lies quietly with eyes closed and disappearing if the attention is fully occupied. Berger records it by pad electrodes on the scalp or, preferably, by needles reaching the periosteum of the skull. He finds that the waves

are larger when the needles are over an opening in the skull than when they are over the intact bone. From this and other evidence he concludes that the potential changes are produced by the cerebral cortex, and that they represent a fundamental activity of the brain.

During the same period a number of workers have recorded the potential changes which take place in the exposed cortex of animals. Their findings have been difficult to reconcile with Berger's as the potential changes have been much less regular and have rarely shown any sign of a persistent rhythm at 10 a second. Our own work on animals (Adrian and Matthews, 1934) led in the same direction. We found it difficult to accept the view that such uniform activity could occur throughout the brain in a conscious subject, and as this seemed to us to be Berger's conclusion we decided to repeat his experiments. The result has been to satisfy us, after an initial period of hesitation, that potential waves which he describes do arise in the cortex, and to show that they can be explained in a way which does not conflict with the results from animals.

The present paper is chiefly concerned with the nature of the potential waves, the structures responsible for them and the kind of activity which they represent. To anticipate it may be said that we regard the effect as due to a spontaneous rhythmic activity of a group of cortical cells in some part of the occipital lobe. These tend to beat synchronously when they are undisturbed, but visual activity or widespread non-visual activity in the brain breaks up the rhythm by exposing the cells to a mosaic of excitations which makes synchronous action impossible. Berger, if we have interpreted him correctly, regards the waves as having a much wider and less specific origin, but the evidence as to localization is the only important point on which our results seem to differ from his.

Since the effect is so characteristic we shall refer to it in future as the Berger rhythm. Berger calls it the *electrencephalogram*, but the shorter title avoids the suggestion that the rhythm is produced by the entire cortex.

TECHNIQUE.

As the potential waves are of the order of $\frac{1}{10}$ mv. or less they are most conveniently recorded by a valve amplifier leading to some form of oscillograph. To record their exact form and to detect very rapid oscillations as well (e.g. those from muscle) we have used the Matthews oscillograph with a period of $\frac{1}{2000}$ a second recording optically on bromide paper. In the majority of experiments, however, a very high period in the recording instrument is unnecessary and we have found it more convenient to use the Matthews ink-

writer oscillograph which has a period of $\frac{1}{10}$ second. For this we have generally used a balanced input amplifier (Matthews, 1934) followed by two condenser coupled valves leading through a tapped volume control to the second of the three valves of the oscillograph amplifier. The condenser coupling was usually arranged so that slow potential changes would not appear in the record, but controls have been made with amplifiers capable of handling very slow changes without distortion. It is sometimes an advantage to be able to hear as well as see the rhythm; although its frequency is only 10 a second it can be made audible by using a horn loud speaker with the diaphragm set very close to the pole pieces and a condenser in parallel to cut out high frequencies.

As electrodes we have used squares of copper gauze covered with lint and soaked in warm saline. These are fixed in position by a head bandage, the hair under them being parted so as to ensure that they make good contact with the scalp. Since the amplifier takes no appreciable current from the electrodes the precise value of the skin resistance does not affect the size of the potential waves. In a few preliminary experiments we followed Berger's technique, using steel needles thrust through the scalp, but we were relieved to find that pad electrodes gave equally good results. Berger stresses the importance of absolute quiet and keeps the subject on a couch in a room separate from the recording system. In the laboratory, with research workers as subjects, good rhythms can usually be obtained with the subject sitting in a chair, though complete relaxation of the neck muscles has the advantage of giving a smoother base line. In certain experiments (e.g. with blind patients) the room was kept as quiet as possible and the subject lay on a bed.

THE ORIGIN OF THE RHYTHMIC POTENTIAL WAVES.

Fig. 1 gives typical records of the Berger rhythm made with pad electrodes on the vertex and occiput and fig. 2 shows the essential condition for its appearance, namely that there should be an absence of visual activity¹: thus in fig. 2, A and B it develops on closing the eyes, in fig. 2, C it disappears when they are opened in a lighted room and in fig. 2, D it is present when they are open in the dark. There is often more variation in the size of the waves and sometimes the rhythm only appears intermittently, but its frequency is so characteristic and so constant that there is never any doubt as to its presence. With pad electrodes the potentials are at a maximum of about $\frac{1}{10}$ mv. when one of the pads is just above the external occipital protuberance and the other is 3 in. or more away. What evidence is there to show that these potentials are developed in the brain?

Berger has discussed the evidence very fully and has carried out

¹ More correctly, an absence of the activities connected with pattern vision (see p. 367, paragraph 2).

numerous controls. The most direct proof of a cerebral origin is his finding that with needle electrodes the potentials are largest when the needles pierce the scalp over an opening in the skull. This is perhaps

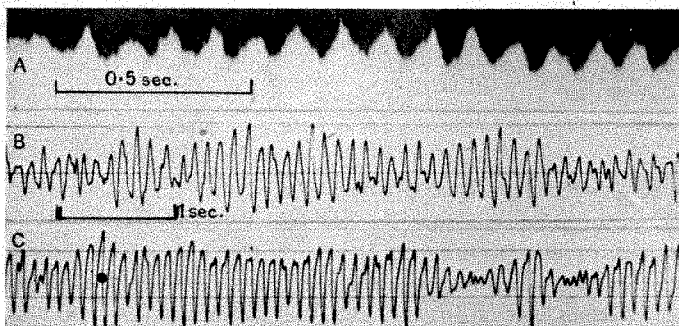


FIG. 1.—Records of the Berger rhythm made with pad electrodes on the head (vertex and occiput), the subjects sitting with eyes closed.

- A. Subject E. D. A. Record made with Matthews' oscillograph, period $\frac{1}{8000}$ sec. Maximum excursion 0.07 mv. Frequency 9.5 per sec.
- B. Subject W. H. Record made with ink-writer oscillograph, period $\frac{1}{40}$ sec. Frequency of waves 9 per sec.
- C. Subject K. Y. Record made as in B. Frequency 10.5 per sec.

N.B.—All ink-writer records are at the same speed. Of the subjects examined by us, W. H. gives the slowest and K. Y. the most rapid rhythm.

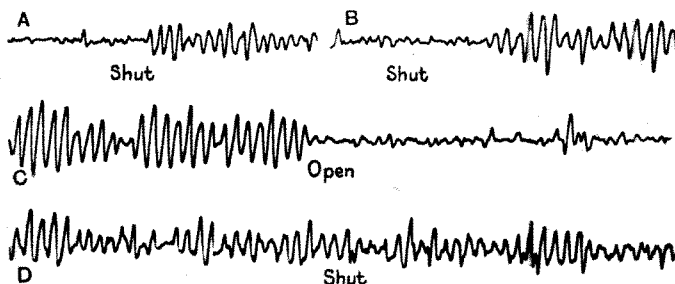


FIG. 2.—The development of the rhythm in the absence of visual activity.

- A. E. D. A. The rhythm appears when the eyes are closed.
- B. B. H. C. M. Ditto.
- C. E. D. A. The rhythm disappears when the eyes are opened.
- D. W. H. After some minutes in the dark the rhythm is present with the eyes open. Closing them does not alter the rhythm.

enough in itself, but we were unconvinced until we had satisfied ourselves (a) that the waves are not due to the eye muscles or to movements of the eyeballs and (b) that there is no need to postulate an origin from the whole surface of the brain, but only the occipital lobe. The discussion of these two points will show the general nature of the problem and of the evidence at our disposal.

Evidence against an orbital origin.—The chief source of uncertainty can be seen from the diagram in fig. 3. The skull forms a box with walls of relatively high resistance and the scalp is a thin sheet of conducting material leading to the various muscles of the face and neck. Thus a contraction of almost any of them can give rise to potential oscillations between electrodes on the scalp and a muscle like the temporal or occipito-frontalis can give oscillations much larger than the waves of the Berger rhythm. Fortunately the electromyogram of a normal sustained contraction is a rapid irregular affair quite unlike the 10 a second rhythm; but the muscles cannot be ruled out altogether, for waves of the required form and regularity might be produced by a clonus or tremor in which all the motor units contract synchronously.

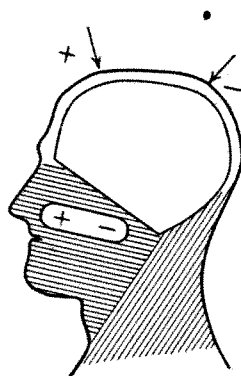


FIG. 3.—Showing how electrodes in the scalp may be affected by action currents in the face and neck owing to the high resistance of skull.

The most likely place for such a clonus is the orbit. The Berger rhythm is obviously connected in some way with the visual mechanism, and in all the conditions in which it appears there is a lack of ocular fixation. It is possible that shutting the eyes or the presentation of a uniform field would allow some of the eye muscles to develop a rhythmic beat. This would disappear as soon as the visual attention was aroused and it would give regular potential waves in the muscles.

For a time we suspected that the rhythm arose in this way, but it was soon clear that the external eye muscles are so deeply buried in the orbit that their action currents can have little effect on electrodes applied to the scalp. We found that active and passive movements of the eyeball were equally ineffective: with the electrodes on occiput and vertex the jerky eye movement produced by looking at the spokes of a revolving wheel gives no corresponding potential waves, and

an oscillation of the eyeball by a clockwork-driven rod has no detectable effect though the eyeball is moved through several degrees.

Again, the rhythm is not dependent on a particular posture of the eyes (for it can occur with the lids open or closed) and is not necessarily interrupted by eye-movements. When the eyes are open in the dark and the rhythm is well developed, a movement of the eyes to left or right or a closure of the lids will cause no break in the sequence of waves (fig. 2, D). Blinking or firm closure of the eyelids may produce large potential changes, for the orbicularis is a surface muscle, but we have failed to produce any evidence of potential changes due to the eyeball or its muscles. And in any case the potential gradients would be at a maximum in the neighbourhood of the eye, whereas the waves of the Berger rhythm are at a maximum over the occipital part of the skull.

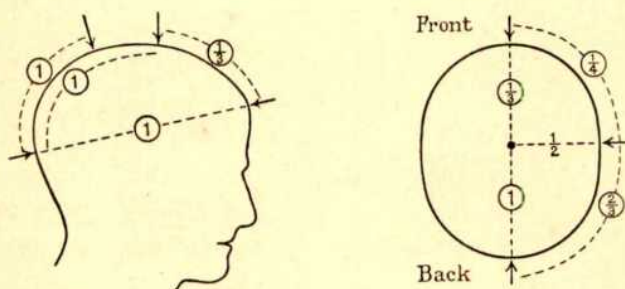


FIG. 4.—Rough estimate of average size of waves with different electrode positions in subject W. H.

Localization of potentials.—The distribution of the potentials over the head is a point of great importance, both for the exclusion of eye movements and for deciding the part of the brain responsible for the rhythm. Berger seems to believe that every part of the cortex may contribute to the potential changes (Berger, 1933A, fig. 3, &c.), and it is true that the waves can be detected in almost any part of the scalp; but in every case examined we have found that to produce the maximum amplitude one of the electrodes must be slightly above the external occipital protuberance. The position of the other is then immaterial provided that it is at least 3 inches away.

Since the waves vary in size from moment to moment it is impossible to make an accurate comparison of different electrode positions, but the diagrams in fig. 4 give a rough estimate of the relative sizes and the records in fig. 5 show the kind of data on which the

diagrams are based. It will be seen that with one lead on the vertex and the other on the forehead the waves are on the average one-half or one-third as large as they are with the leads on vertex and occiput. With both leads near the eyes the rhythm can rarely be detected at all. These facts are definitely opposed to the idea that the rhythm arises from structures in the orbit. They cannot be taken as a conclusive proof of origin from the occipital lobes rather than some other part of the brain, for the distribution of potential gradients outside the skull might depend on the thickness of the bone, the presence of blood sinuses, &c., in different regions. The best proof that the waves do in fact arise in the occipital part of the brain comes from patients

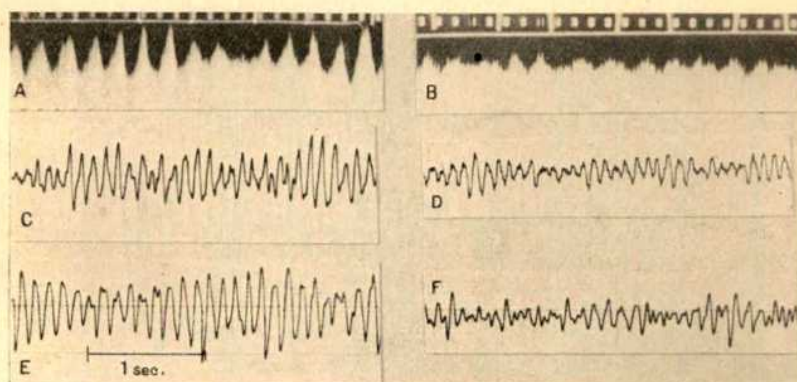


FIG. 5.—Comparison of waves recorded from the back and front of the head in different subjects.

- A. E. D. A. Electrodes on vertex and occiput. B. On vertex and forehead.
C. C. L. P. Vertex and occiput. D. Vertex and forehead.
E. W. H. Vertex and occiput. F. Vertex and forehead.

In record B the small, rapid excursions are due to muscle action currents.

with openings in the skull and is dealt with on p. 363, where the distribution of potential is considered in more detail.

Evidence against cranial muscles, &c.—Some time has been spent in discussing eye movements as a possible cause of the rhythm because there is no doubt that the eyes are somehow concerned in it. An oscillation of the eye muscles or eyeballs is therefore the most likely cause apart from the brain. If the eyes are ruled out there is still the possibility of a tremor in the muscles of the neck, face, or scalp, but it would be difficult to explain why the eyes must be inactive and still more to explain our failure to influence the rhythm by changing the posture of the head or contracting facial or neck muscles. The head

may be bent forward or back, but the 10 a second rhythm still appears when the eyes are closed and goes when they are opened to the light. If the neck muscles are contracted the rhythm is superimposed on an electromyogram of the usual type but there is no sign that it is altered in any way. The forehead may be wrinkled or the scalp pulled without affecting it.

Other possibilities, e.g. the pulsation of vessels, activity of pilomotor muscles, tremors of the head, &c., have been examined by Berger and rejected. We have considered the possibility of the waves being due to retinal potentials of some kind, but find that electrodes on the scalp

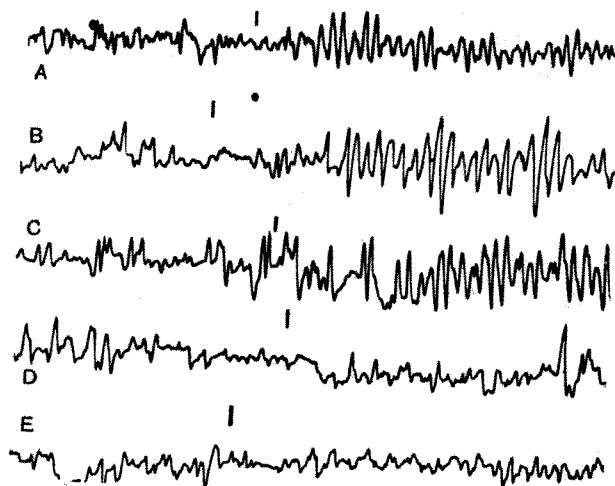


FIG. 6.—Records from patient with bone defect in the right temporal region due to shell wound seventeen years ago. The eyes are closed at the signal.

- A. Electrodes on occiput and left parietal region.
- B. „ „ occiput and right parietal region.
- C. „ „ occiput and forehead.
- D. „ „ forehead and left parietal region.
- E. „ „ forehead and right parietal region.

cannot even pick up the potential change caused by illuminating the eye suddenly with a bright light.

Evidence in favour of the cortex.—Besides this negative evidence against an extracranial origin there is positive evidence in favour of the brain, derived from subjects with openings in the skull. Berger has examined many of these with needle electrodes in the scalp and finds that the waves are always larger when the needles are over the bone defect, wherever it may be. If the currents arise somewhere inside the skull this result is to be expected, but if they arise outside and are

conducted to the electrodes by the scalp the defect in the skull should produce greater short-circuiting and smaller potential changes.

Our own observations on trephined patients lead to the same conclusion but are chiefly interesting for giving more definite evidence of localization. We have had two patients with small bone defects in the temporal region, one the result of a shell wound and the other an exploratory opening for a condition which developed no further. In both patients the rhythm on closing the eyes was well marked when an occipital electrode was used, but if the electrodes were further forward (e.g. on vertex and forehead) the waves were completely absent (fig. 6). If the skull had been intact they would have been merely reduced in size (cf. fig. 5). Thus the opening in the skull has the effect of confining the potential changes to the back of the head. If the waves have an extracranial origin or an origin from the whole cortex it is hard to conceive any reason for this, but if they come from the occipital part of the cortex the reason is clear enough.

The distribution of current with the skull intact or trephined can be illustrated by rough diagrams, though it must be understood that these can make no claim to take every factor into account. We may start with the assumption that the cortical potentials are due to structures close to the surface of the brain and directed at right angles to it, for the potentials recorded from the exposed cortex are best explained in this way (Adrian and Matthews, 1934). Now, if the skull were a sphere, an area of electrically active cortex would give the distribution of current shown in fig. 7, A, the lines of current flow diverging from a region opposite the active areas.¹ Actually, with the skull intact, the divergence takes place somewhere in the frontal region (fig. 7, B), but there is usually enough difference of potential between vertex and forehead to enable the waves to be recorded there. An opening in the skull will modify the distribution in the way shown in fig. 7, C. The circuit within the brain to the opening and then back in the scalp to the occiput involves only one thickness of bone and so offers a pathway of relatively

¹Owing to the relatively high resistance of the skull the current will be much more evenly distributed than it would be if the brain, skull and scalp were all the same conductivity. In a homogeneous medium the current flowing along any path would be inversely proportional to the length of the path; thus the lines of current flow would be concentrated in the occipital region. But it will be seen from fig. 7, B that except at the margins of the active region the current must pass twice through the skull to complete the circuit. The soft tissues will contribute a relatively small proportion of the total resistance, and therefore the length of the pathway through them will be relatively unimportant. Thus the longer pathways (through the frontal and parietal bones) will carry an appreciable fraction of the total current.

low resistance from the interior to the active surface: the result is that a negligible proportion of the current will flow through the scalp anterior to the opening.

Three patients with suboccipital decompressions gave evidence of the same kind. In their case the rhythm could not be obtained at all unless one of the electrodes was on the occiput very close to the opening in the bone. As in fig. 7, c, the opening becomes the main pathway from the interior of the brain to the active surface, and, as the active surface is very close to the opening, the potential gradients will be relatively steep in this region but inappreciable over the rest of the skull.

The potential distribution in these cases shows that the active area is somewhere in the occipital region, but the main focus of activity is

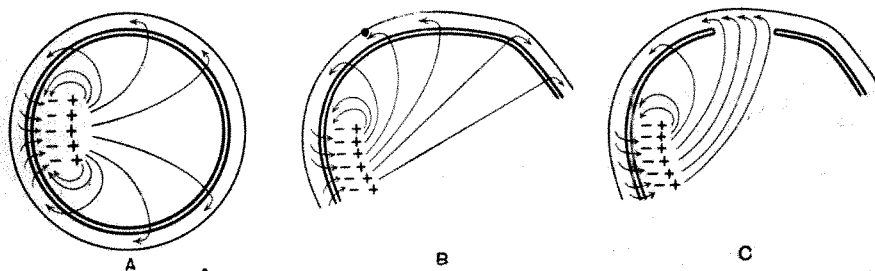


FIG. 7.—Diagrams to show current distribution—A, if the skull were spherical; B, in the median plane with the skull intact; and C, with an opening in the skull.

not at a fixed point in the brain. This can be inferred from records made with two oscillographs leading simultaneously from different regions of the skull. Berger has made many of these and has shown that the relative size of the waves from the different leads is by no means constant. The same result can be seen in fig. 8, A which gives simultaneous records of the potentials between vertex and occiput and vertex and forehead. The relative size of corresponding waves in the two records varies considerably and occasionally the potential change between vertex and forehead is larger than that between vertex and occiput.¹

A result of this kind can only mean that the distribution of current flow in the brain shifts from time to time, but it is not at all incompatible with the view that the activity arises in the occipital region.

¹ The absence of a fixed ratio between corresponding waves from the two pairs of leads accounts for the fact that in records made with the electrodes on occiput and vertex the waves are neither consistently larger or consistently smaller than in records from occiput and forehead (cf. fig. 4). The general direction of current flow in the frontal region varies to some extent with the individual and probably depends on the shape of the head.

A reference to fig. 7, A and B, will show that a movement up or down in the position of maximum activity will produce a corresponding movement in the region at the opposite side of the skull from which the lines of current-flow diverge in the scalp. The direction of movement in the two oscillograph tracings in fig. 8, A shows that the potentials at occiput and forehead rise and fall simultaneously relative to the vertex (in agreement with the distribution given in fig. 7, B) but a shift in the point of current divergence will naturally alter the relative sizes of the waves from the two pairs of leads and may suppress or reverse them in one pair of leads while little alteration occurs in the other.

Further complications probably arise from the beat spreading progressively over the active area, or over some part of it, instead of

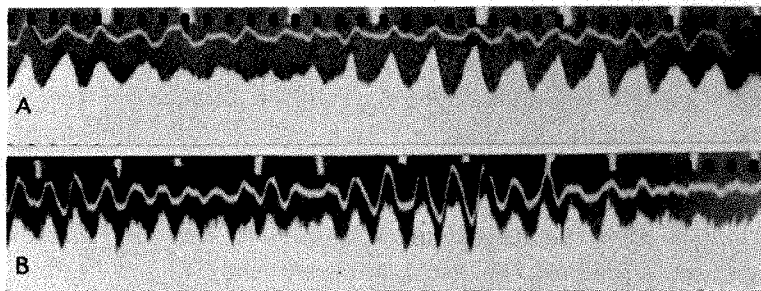


FIG. 8.—Simultaneous records of the waves at two pairs of electrodes.

- A. The white line records the waves between vertex and forehead and the junction between dark and light area records those between vertex and occiput.
- B. The white line records the waves between occiput and right parietal region and the junction between dark and light those between occiput and left parietal region.

appearing simultaneously at every point. In the exposed cortex of animals the large potential changes produced by convulsant drugs are due to waves of activity which travel at a finite rate over the surface (Adrian and Matthews, 1934). Similar waves confined to the occipital region would produce a rhythmic shift in the current distribution corresponding to the rhythmic change in the position of maximum activity, and this might lead to phase differences in the potential waves from different leads.

It will be seen from the diagram that if both pairs of leads are confined to the posterior half of the skull the waves should correspond much more closely. This is found to be so. Fig. 8, B gives simultaneous records, one from electrodes on the occiput and above the right ear and the other from the occiput and above the left ear. The waves

are now almost identical, the potentials at either side rising and falling simultaneously relative to the occiput. This result (from four subjects) makes it unlikely that there is much difference in the phase or extent of the beat in the right and left hemispheres, though occasionally the waves are found to increase in size for a few beats on one side and to decrease correspondingly on the other.

It is to be hoped that a more detailed mapping of the potential distribution over the head from moment to moment will show how far the focus of activity can move. For the present all that can be said is that the active region must cover a fairly large area in the occipital lobe and that it must be close to the surface of the brain. If it were deeply situated the short-circuiting by inactive tissue would be too great to allow the potentials to be recorded through the skull. In general the larger the area involved and the nearer it is to the surface the smaller will be the potential change at each point necessary to set up measurable potential gradients outside the skull. An area one or two inches in diameter might be large enough if all the cells in it were active simultaneously, but this estimate is scarcely more than a guess.

The evidence as to the origin of the potential waves may be summarized as follows:—

(1) The form of the waves makes it unlikely that they are due to muscular contractions of the usual kind, but they might be due to a clonic contraction or tremor.

(2) As the rhythm only appears when there is no ocular fixation, a tremor of the orbital muscles might be responsible.

(3) But rapid to-and-fro movements of the eyes give no corresponding potential waves in the scalp. Also potentials due to the eye muscles would be greatest when one of the electrodes is near the orbit. The waves of the Berger rhythm are greatest when one of the electrodes is near the occiput.

(4) The waves are not due to potential changes in the retina, for these are not large enough to affect electrodes applied to the scalp.

(5) The presence of an opening in the skull modifies the potential distribution in a way which is readily explained if the potentials arise in the brain, but not if they arise outside the skull.

(6) In trephined subjects there is a more definite localization to the occipital region.

(7) The magnitude of the potential waves shows that they are most probably due to the simultaneous or nearly simultaneous activity of a fairly large region on the surface of the occipital lobe.

THE FAILURE OF THE RHYTHM DURING VISUAL ACTIVITY.

The occipital origin of the waves emphasizes their close connection with vision. Berger has shown that the rhythm can be stopped by non-visual activity if the subject's whole attention is involved, but it is stopped far more effectively by a pattern in the visual field, however uninteresting. In fact for the rhythm to appear, either the eyes must be shut, or the central part of the visual field must be uniform and the subject must not examine it too closely.

It is the perception of pattern or the attempt to perceive it that interferes with the rhythm. The perception of light does not affect it: if the eyes are closed the rhythm persists, although the subject is aware that the room is light or dark and can say when the illumination is

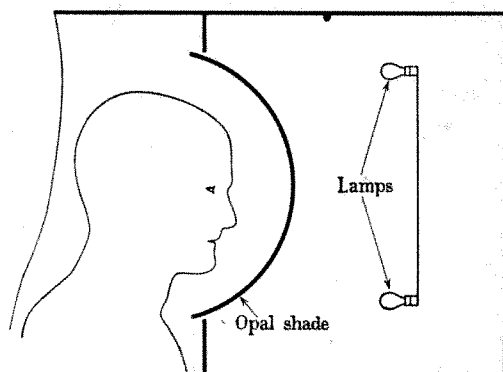


FIG. 9.—Arrangement for giving a uniform visual field with different degrees of illumination.

altered. Again, with the eyes open, the visual field can be made more or less uniform by arranging an opal glass bowl in front of the face and lighting it by a ring of lamps (fig. 9). The rhythm will appear after a time, and when it is established the illumination of the bowl can be varied without causing more than a momentary pause in the waves, provided that the light is not unpleasantly bright. On the other hand, a narrow band of shadow thrown across the field will stop the rhythm at once. Similarly, when the eyes are shut, the circle of light caused by pressure on the eyeball will abolish the rhythm and bright after images will delay its appearance.

Absolute uniformity of the visual field is not essential, however; with the eyes shut the rhythm usually appears a short time before an after image has completely faded, and with the eyes open the peripheral

part of the field may contain some pattern. But sharp contrasts nearer the central part of the field are prohibitive. Thus a few black spots on the opal screen, or a few small holes in the shutters of a dark room, will abolish the rhythm if the subject looks directly at them, but if they come into the peripheral field he may be aware that there is something there and yet the rhythm will persist.

The effect of closing the eyes.—Although there is the same contrast in the effect of a uniform and non-uniform field whether the eyes are closed or open, the closure of the eyes seems in itself to favour the development of the rhythm. The regular waves usually appear half a second or less after the eyes are shut, but if they remain open and the

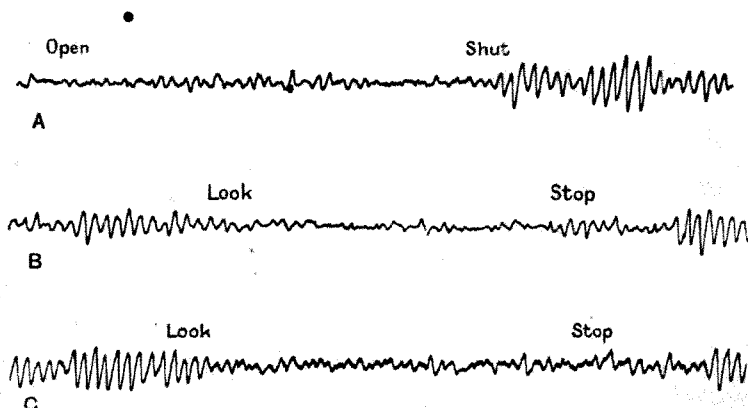


FIG. 10.—Development of the rhythm with the eyes open in the dark. Head enclosed in a box lined with black velvet.

A. During the first few minutes the rhythm only appears when the eyes are closed.
B and C. Later. The rhythm is present with the eyes open but is abolished by trying to see.

field is made uniform the waves may not appear for some minutes. The difference is chiefly noticeable when the subject is first confronted with a uniform field. This may be either the opal screen arrangement or the uniform black field produced by enclosing the head in a box lined with black velvet, or by making the whole room completely dark. To begin with the rhythm will only appear when the eyes are shut (fig. 10, A), and it will cease when they are opened, although the field is uniform. In a few minutes the rhythm will develop with the eyes open. It may still be disturbed when they are opened after a period of closure, but eventually opening them will cease to have any effect.

The most likely explanation is that the act of closing the eyes is coupled with an automatic withdrawal of the attention from visual

phenomena. When our eyes are open we try to see something, even though we are in a room which is too dark for anything to be made out. So with the head before an opal screen or in a dark box the tendency is to look for some trace of detail, and to begin with it is only when the eyes are closed that the subject is completely indifferent to the content of the field. After a time he becomes used to his surroundings and it is easier to open the eyes without expecting and trying to see. It is then that the rhythm persists.

This explanation is based mainly on the introspection of one of us acting as subject. It must be admitted that when the eyes are open in the dark and the rhythm absent the feeling of "trying to see" is often very slight, although at times one may be conscious that one is peering into the blackness. But the explanation is supported by the fact that after the rhythm has become established it can be made to disappear at will by attempting to see some trace of detail in the field (fig. 10, B and C). The attempt is often attended with a feeling of muscular effort which probably implies convergence and accommodation, but the rhythm may go before this is felt.

An effort of the same kind can abolish the rhythm although the eyes are shut. In this case the effort causes a method of convergence which can be felt through the closed lids. But it is perhaps a mistake to group this with the other kinds of visual activity which abolish the rhythm, for it involves considerable mental effort and a non-visual activity of the same kind, e.g. straining the ears to hear a nearly inaudible sound (e.g. a watch ticking), is equally effective. On the other hand, when the eyes are first opened in the dark no conscious straining to see is needed to prevent the appearance of the rhythm.

In the majority of subjects the rhythm becomes more clearly marked after the examination has lasted ten minutes or more. The improvement seems to be due to the repeated periods with the eyes closed. But if they remain closed for a long period the rhythm often becomes more intermittent. It is at its best, with large waves and little fluctuation in size, immediately after the eyes have been opened and closed again—as though the sudden disappearance of the normal visual activity gives the most favourable conditions. This at least is our impression, though the variations from subject to subject and from time to time are too great to allow of any certainty.

Absence of rhythm in blind subjects.—One set of observations supports the impression that the rhythm would not persist indefinitely if the eyes remained closed. We have examined three patients who

have been totally blind for some years and we have been quite unable to detect any sign of the rhythm in them. In one of them (blind for thirty-five years from an accident, with hæmorrhages in the vitreous, &c.) the eye movements were unusually good but closing the lids did not produce the rhythm. Another was a case of double optic atrophy of two to three years' duration, and the third had had both eyeballs removed in 1918 as the result of a shell wound. They were examined lying on a couch in a quiet room, but we could not discover any condition which would cause the rhythm to appear.

The bearing of this result on the cortical mechanism of the rhythm will be discussed later. It is scarcely surprising, for if the most favourable conditions are those which exist just after pattern vision ceases, we might expect that the rhythm would be absent in patients whose pattern vision ceased long ago.

THE EFFECT OF NON-VISUAL ACTIVITY.

In regard to activities other than visual we have little to add to Berger's account. We find, as he has done, that a problem which claims the whole attention will abolish the rhythm though the eyes are shut. A difficult question in mental arithmetic will do so as long as the subject tries hard to solve it (fig. 11, A), but the rhythm will return as soon as his attention wanders. In the same way an attempt to tie or untie as many knots as possible in a given time will abolish the rhythm as long as the subject concentrates his whole energy on the task.

As regards sensory stimulation, the effect seems to depend mainly on the amount of disturbance produced in the subject's mind (or on the amount of "affect"). An unexpected touch by the experimenter in an unexpected region (e.g. the face) will usually stop the waves (fig. 11, B), but the subject can touch his own face or inflict considerable pain on himself without disturbing it. As might be expected, the disturbing effect of questions, commands, &c., is often most pronounced when a subject is examined for the first time: the records in fig. 11 are from subjects who were quite familiar with the procedure.

It will be clear from this that a great deal can go on in the subject's brain and mind without upsetting the rhythm. He can count numbers aloud, repeat familiar poetry or join in an unimportant conversation with, at most, an initial reduction in the size of the wave. The photographs in fig. 5 are an example of the amount of non-visual activity which can go on without interfering with the rhythm, for they were made by one of us working without assistance and recording the waves

from his own head. It is true that no manipulations had to be made after the eyes were closed, but a restful state of mind was scarcely possible. Again some of the evidence on the effect of opening the eyes in the dark was made by one of us listening to the rhythm from his head in a loud speaker. This made it possible to correlate the impression of not looking or looking with the presence or absence of the rhythm. In this case, as when the eyes are opened in daylight, the subject can hear that the rhythm ceases, for opening the eyes does not prevent one from listening; but the non-visual activities which abolish the rhythm demand so much attention that a subject engaged in them

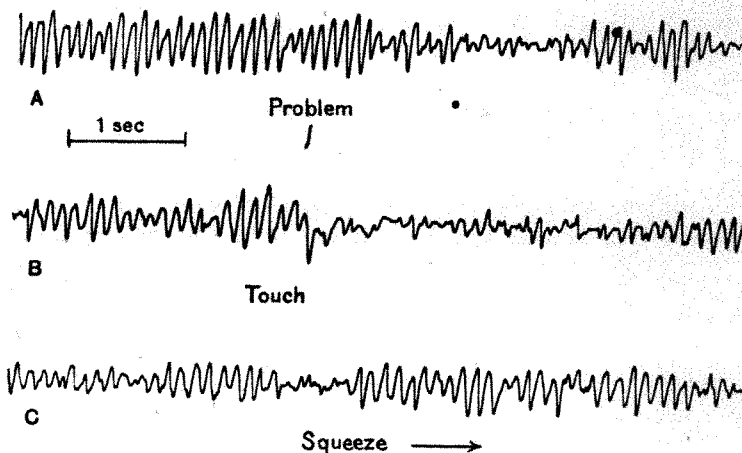


FIG. 11.—A and B. Abolition of the rhythm by non-visual activities.

A. E. D. A. Eyes closed. Problem in mental arithmetic given at signal.

B. W. H. Eyes closed. Touch on the nose with cotton-wool.

C. Persistence of rhythm in spite of muscular effort.

W. H. Eyes closed, squeezing pliers as tightly as possible.

cannot listen at the same time and can never hear whether the rhythm has been affected or not.

It is interesting to find that powerful muscular contractions do not interfere with the rhythm although the subject exerts his full strength. Thus in fig. 11, c, gripping a pair of pliers as tightly as possible seems, if anything, to reinforce the waves. But a powerful muscular effort need not engage the entire attention, for it is possible to listen to the rhythm whilst the effort is made.

THE CORTICAL MECHANISM OF THE RHYTHM.

The general nature of the Berger rhythm seems to be fairly clear though several points are still obscure. We have to account for a

pulsating activity which develops in the occipital lobe and involves a considerable number of neurones working synchronously. These beat together with a fixed period, but they can only do so when pattern vision is absent.

Now synchronous activity can only occur in a group of neurones when the conditions of excitation are uniform throughout the group. When this obtains the neurones will all discharge at the same frequency and they may come to work in phase with one another as a result of their interconnection. For instance, the vertebrate retina (Adrian and

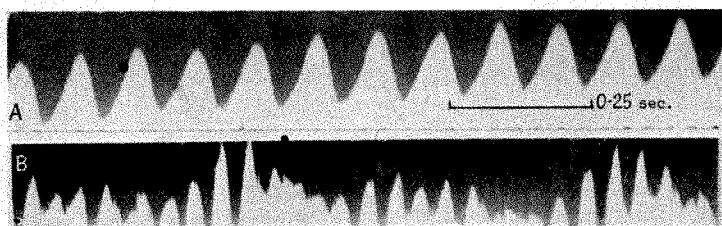


FIG. 12.—Records of potential changes from eye and optic ganglion of water-beetle (*Dytiscus marginalis*). Above, eye in the dark, waves at 9 a sec. Below, eye exposed to bright, uniform light, waves at 20 a sec.

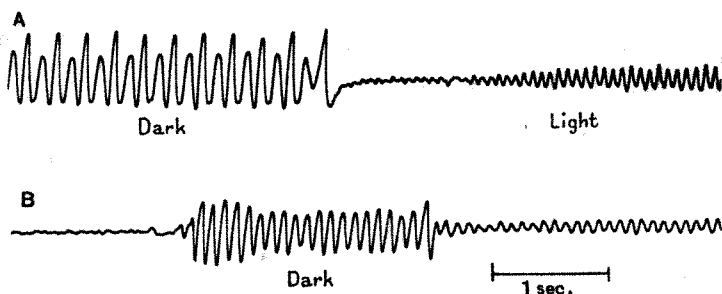


FIG. 13.—Eye and optic ganglion of water-beetle. Records showing the effect of different kinds of illumination.

- A. Eye in the dark and then exposed to bright, uniform light. Waves at 8 a sec. in the dark and at 14 a sec. in the light.
- B. Another preparation. Eye first exposed to medium non-uniform illumination (no waves), then in dark (waves at 10 a sec.), then to feeble non-uniform light (waves still at 10 a sec. but of much smaller amplitude).

R. Matthews, 1928) or the invertebrate optic ganglion (Adrian, 1932) may give a rhythmic electric pulsation when the eye is very brightly and uniformly illuminated and sometimes a rhythmic pulsation at a lower frequency when the eye is in darkness (fig. 12). In both conditions the neurones can pulsate synchronously because the degree of excitation is the same for all of them; but non-uniform illumination of medium brightness makes the synchronous beat impossible and abolishes the rhythmic potential waves (fig. 13).

The disorganization of a synchronous beat in the cortex is illustrated in fig. 14. This record is from the exposed brain of a rabbit under light urethane anaesthesia. The large waves represent periods of wide-spread activity due, probably, to the spontaneous discharge of the cortical neurones. At the signal the foot is pinched, and with the arrival of afferent impulses the cortical beat breaks up into small irregular



FIG. 14.—Potential waves from exposed cortex of rabbit under urethane. At the signal the foot is pinched and the waves break up into rapid asynchronous activity.

oscillations of high frequency—the sign of asynchronous action. The record is also an illustration of the general tendency for cortical neurones to discharge spontaneously when they are undisturbed. The cells of the respiratory centre give the best example of a spontaneous beat, but the cortical neurones are equally unable to remain for long without discharging, and electrical records show them to be in constant activity as long as they are supplied with oxygen.

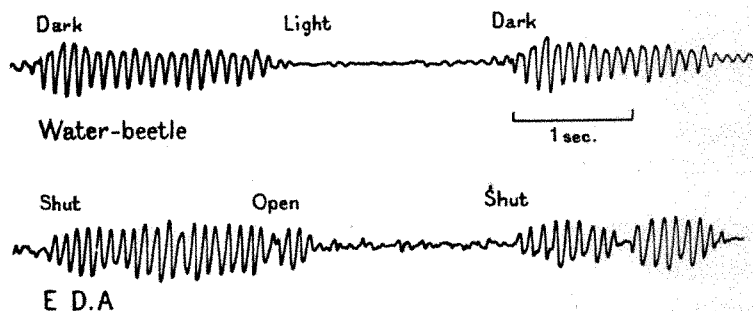


FIG. 15.—Comparison of waves from water-beetle preparation in darkness and light (upper record) and from human subject (E. D. A.) with eyes closed and open (lower record). In both the rhythm is abolished during visual activity.

The Berger rhythm has a fixed, low frequency, and appears in or near the visual part of the cortex in the absence of visual stimulation. Thus it most probably represents a spontaneous beat in a group of cortical neurones, a beat comparable to that of the water-beetle eye in darkness. There is, in fact, a surprisingly close resemblance in the records from man and from the water-beetle, for the frequency of the spontaneous beat happens to be much the same in both (cf. fig. 15).

The abolition of the rhythm by pattern vision represents the change from synchronous to asynchronous action; this would follow from the disturbing effect of a mosaic of excitations in the optic tract. In the same way the invasion of the beating area by widespread cortical excitations would prevent synchronous action although the visual field was uniform, and this would account for the effect of intense non-visual activities.

The difficulties begin when we attempt to decide the exact position and function of the area. It is in the occipital lobe and it is concerned with vision, but it is unlikely that it is the striate area itself. Many investigators have recorded the electric responses of the striate area and found the most prominent to be a large potential change when the eye is illuminated and another when it is darkened. With electrodes arranged on the head for recording the Berger rhythm there is no "on" and "off" effect of this kind, and indeed the position of the striate area makes it unlikely that potentials arising in it could be detected through the skull.

The area seems to have little or nothing to do with the perception of light, for the period of the waves is not altered by a change in the amount of light falling on the closed lids and the subject can notice the change without abolishing the rhythm. The area is not concerned with visual imagery, for the rhythm is unaffected by visualizing shapes, figures, &c. It is concerned with pattern vision, but the rhythm can be abolished by attempting to see a pattern as well as by the sight of one.

This complicates the issue by giving us two possible factors which may interfere with the synchronous beat. The absence of the rhythm when the eyes are first opened in a dark room seems to depend not on inequalities in the field but on the direction of a certain amount of attention to it. It is possible, therefore, that a pattern in the field abolishes the rhythm because it attracts the attention and not because it excites the area unequally. This, in fact, is the explanation given by Berger. The effectiveness of a pattern in abolishing the rhythm seems to depend entirely on the amount of sharp contrast in the central part of the field, but it is arguable that this determines the amount of attention which the pattern will attract.

The point is not worth elaborating until we have some idea of the neural processes which may be involved in attention. It is clear, however, that the area which gives the rhythm is concerned specifically with visual activities and is not some general correlating centre. As

was pointed out on p. 371 the visual activities which abolish the rhythm do not claim more than a small part of the subject's attention and if pattern vision is absent the rhythm persists in spite of other activities which demand a fair share of attention for themselves. It is clear, too, that the part of the brain concerned with vision would be the most likely place for a spontaneous beat covering a wide area. By shutting the eyes we can cut off the stream of impulses which enter the occipital lobe from the million fibres of the optic nerve. The visual areas of the cortex will be suddenly cut off from afferent excitation and left to themselves will be free to beat spontaneously. There is no other part of the brain in which so large an area could be so readily isolated from external influence, for vision is not only our most important sense but it is the only sense which can be turned on and off at will. It may be added that man is the animal most likely to show the Berger rhythm, for it is in man that the visual part of the brain reaches its highest development.

We have assumed that the area is so much a part of the visual apparatus that when vision is cut off there will be nothing left to disturb it. But an intense activity in the rest of the brain will do so, and it seems that if vision is permanently cut off the area is not allowed to remain idle but becomes gradually more and more accessible to excitations from other parts. In the end it will be continually disturbed and will have no chance of developing a synchronous beat. Thus the Berger rhythm is absent in the blind.

POTENTIAL CHANGES IN THE EXPOSED CORTEX.

It has been pointed out that the potential changes which can be recorded from the surface of the head in man bear little resemblance to those from the exposed cortex in animals. This may be due partly to the greater importance of vision in human behaviour and the greater size of the visual regions in the human brain. In cats and rabbits, for instance, the area which corresponds to that giving the Berger rhythm in man is certainly much smaller if it exists at all. It will therefore be much more exposed to disturbing effects from the neighbouring cortex and these may always prevent the spontaneous activity of the cells from developing into a synchronous beat.

There is, however, another reason for the different character of the records from animals, namely that these are made with electrodes leading directly from the exposed cortex, whereas in man the electrodes are separated from the cortex by the high resistance of the skull. This

arrangement is equivalent to one without the high resistance layer but with the electrodes at a much greater distance from the surface of the cortex. It can give a bird's-eye view, so to speak, of the cortical activity, showing the average potential changes of large areas but nothing of the local detail. With electrodes on the cortex the local detail has much greater prominence and may fill the picture to the exclusion of the general view. Thus surface electrodes on the forehead and vertex can record the Berger rhythm due to widespread pulsation in the occipital lobes, but cannot show anything of the more localized activities taking place in the brain immediately beneath them. On the other hand electrodes on the exposed cortex may show such large potential changes due to local activity that the Berger rhythm would have no chance to appear.

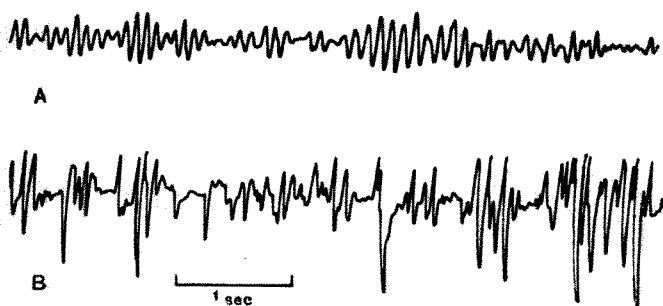


FIG. 16.—Records from the exposed cortex of a patient during an operation for removal of a tumour. A, before removal, cortex oedematous, typical Berger rhythm. B, after removal of tumour and recovery of circulation in the cortex, large irregular waves (the oscillograph is shunted to one-fourth of its former sensitivity).

This may be illustrated by some observations made on the exposed cortex of a patient of Mr. Cairns, who very kindly allowed us to take records during an operation. The patient was a woman with symptoms of a tumour in the right parietal region. When the skull was opened (under local anaesthesia) the exposed cortex was oedematous and the vessels congested. At this stage thread electrodes on the surface of the cortex showed the Berger rhythm and nothing else (fig. 16, A). Mr. Cairns then removed a large neoplasm which infiltrated the cortex in front of the area we had examined. After the removal and about one and a half hours after the first record the electrodes were replaced on the cortex. The oedema and congestion had disappeared and the vessels pulsated well. The record now showed no sign of the Berger rhythm but instead was made up of much larger, irregular oscillations,

like those which can be recorded from the exposed cortex of a cat or rabbit (fig. 16, B).

The obvious explanation of these results is that when the first record was taken the cortex under the electrodes was completely inactive and behaved like so much inert connective tissue. Electrodes on it picked up the Berger rhythm as they would have done if they had been applied to the scalp outside. But with the recovery of the circulation the cortex regained its normal activity, and so at the second recording the local action potentials were so large that the Berger rhythm had no chance of showing itself.

It is clear that further work on the exposed cortex is needed to give a completely satisfactory account of the rhythm. Some uncertainty will remain until it has become possible to localize the beating area, to compare its reactions with those of the striate area, &c. Unfortunately the occipital region in man is very seldom exposed; for the present therefore all that can be said is that records from the exposed brain do not conflict with the view that the rhythm arises in the occipital cortex.

THE RESPONSE TO FLICKER.

The foregoing account of the mechanism of the Berger rhythm is supported by the discovery that regular potential waves at frequencies other than 10 a second can be induced by flicker. If a group of cells tends to beat spontaneously it should be possible to induce a beat at a higher rate by rhythmic stimulation. Accordingly we have tried recording the potentials from the head when the eyes are exposed to a flickering field, and we find that it is possible in this way to obtain rhythms as high as 25 a second.

To produce the response the flicker must involve a considerable part of the visual field. If it is limited to the central part of the field the potential changes are as small and irregular as they are with pattern vision. In the arrangement we have used the subject sits as in fig. 9 with the eyes at the centre of an opal glass bowl and the head covered by a black velvet curtain. The convex surface of the bowl is lit by a 30-watt headlight bulb placed 12 in. away behind a sector wheel, 2 ft. in diameter, rotated by a gramophone motor. The sector wheel gives eight light and eight dark intervals of equal length in each revolution. As the speed at the periphery is high and the distance from the filament very small, the light or shadow takes an inappreciable time to spread over the bowl. The field is brighter at the centre than at the periphery, but unless patterns are deliberately introduced it is uniform enough to allow

the Berger rhythm to develop with the eyes open and the light steady.

Typical records of the response to flicker are given in fig. 17. At the beginning there is the usual 10 a second rhythm, for the eyes are closed and the light is cut off by a shutter. At a signal the eyes are opened and the shutter lifted to turn on the flickering light. The result is a series of potential waves having the same frequency as that of the flicker.

To obtain this result the intensity of the light has to be carefully adjusted. If it is too dim the sensation of flicker soon dies away and the rhythm reverts to 10 a second. If it is too bright the field may become filled with coloured patterns, the sensation is extremely

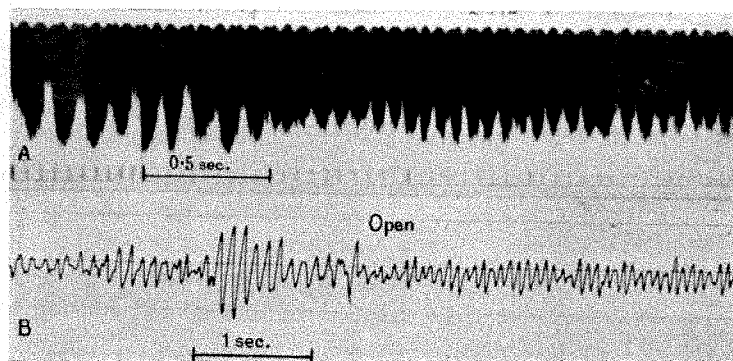


FIG. 17.—Potential waves produced by exposing the eyes to a uniform flickering field. Each record begins with the eyes closed to show the usual 10 a sec. rhythm.

A. E. D. A. Flicker at 16 a sec.

B. C. L. P. Flicker at 14 a sec.

unpleasant and no regular waves are obtained. But it is usually possible to find an intensity which will at the worst give occasional patches of the flicker rhythm; more often the rhythm is clearly marked when the eyes are first opened and becomes intermittent after a time, but is never absent for more than a second or two.

Controls have been made to ensure that the potential waves are not artefacts due to induced effects from the sector wheel or its motor or to the flickering light acting directly on the electrodes. The latter possibility is ruled out by covering the head with several layers of black velvet to exclude any stray light which might reach the electrodes. The wheel and motor are not responsible as they are kept running throughout the experiment, whereas the rhythm only appears when the eyes are open. It can be shown also that the potential waves of the

flicker response come from the same part of the head as the waves of the Berger rhythm, for the relative sizes of the two remain the same when the position of the electrodes is changed, although the absolute size varies greatly (fig. 18). This does not prove that they arise from

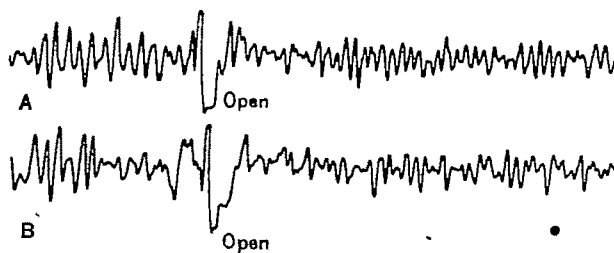


FIG. 18.—Records showing that the relative size of the waves of the Berger rhythm and of the waves due to flicker remain the same for different positions of the electrodes. Subject E. D. A. Signal line shows frequency of flicker.

- A. Electrodes on vertex and occiput. Half way through the eyes are opened to a field flickering at 14 a sec.
- B. Electrodes on forehead and vertex. Sensitivity increased to make the waves of the Berger rhythm equal to those in record A. Eyes opened to flickering field as in A.

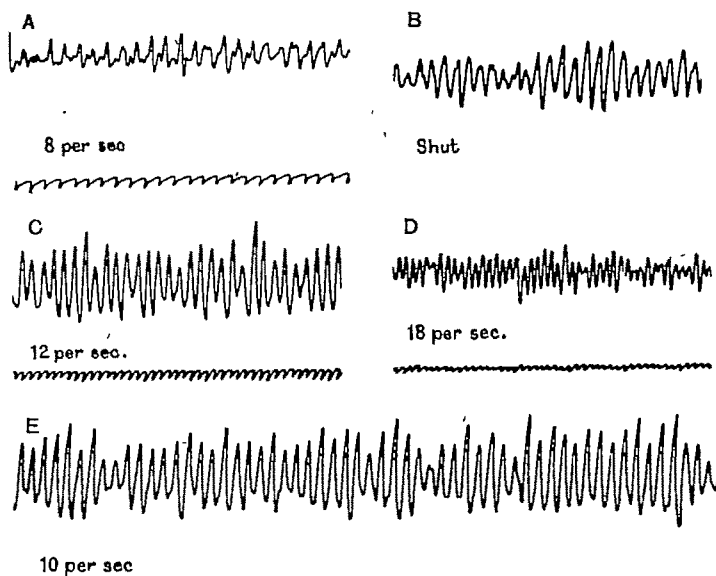


FIG. 19.—Examples of different rhythms induced by flicker. Subject E. D. A. Signal line shows frequency of flicker.

- A. Flicker at 8 a sec.
- B. Eyes closed and field dark. Berger rhythm at 10 a sec.
- C. Flicker at 12 a sec.
- D. Flicker at 18 a sec.
- E. Flicker at 10 a sec. Compare with B.

exactly the same area but shows at least that the flicker response must come from the occipital lobe, if the Berger rhythm does so. The existence of the flicker response may be taken as an additional argument against the view that these potential changes are due to eye movements. There is certainly no visible oscillation of the eyeball when the response is present: a tremor of the external ocular muscles is possible, but the evidence on p. 359 shows that this could scarcely account for the potentials.

The flicker rhythms are shown most clearly with rates between 10 and 20 a second (fig. 19). We have not tried rates higher than 25 a second as the apparatus could not be run comfortably at higher speeds. With rates between 7 and 10 a second the flicker rhythm is sometimes

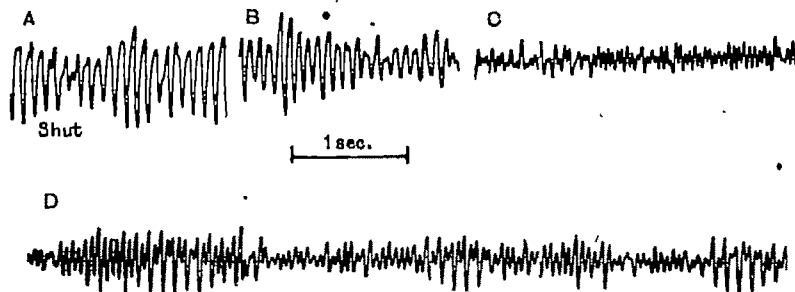


FIG. 20.—Rhythms of double and half the rate of the flickering light. Subject K. Y.

- A. Eyes closed, field dark. Berger rhythm at 10.5 a sec.
- B. Flicker at 12 a sec. Waves at the same rate.
- C. A few seconds later. Waves now at 24 a sec. with occasional reversion to the 12 a sec. rhythm.
- D. Flicker at 18 a sec. Large waves at 9 a sec.

quite clear, but the intensity of the light needs careful adjustment. With flicker in the neighbourhood of 20 a second there is in some subjects a tendency for the waves to occur at half the rate (fig. 20, D). More rarely the rhythm becomes twice that of the flicker, though only for short periods at a time (fig. 20, C).

When the flicker is in the neighbourhood of 10 a second the results are unexpected, for it is, if anything, more difficult to obtain a regular series of waves. If the flicker rate is slightly slower or faster than the Berger rhythm there are often periods of complete irregularity, but if the rate is adjusted very carefully in the hope of making it coincide exactly the waves may become extremely regular and may continue for many minutes without the usual waxing and waning in size. The subject is not conscious of any change in sensation when the regular

wave train appears. A sample of the rhythm produced in this way is given in fig. 19, F, with a sample of the normal Berger rhythm (with eyes closed) from the same subject. As a rule the waves of the flicker response have less rounded contours besides being more uniform in size. The need for careful and prolonged adjustment of the flicker rate suggests that the rhythmic excitation plays on the area in a way which must antagonize the spontaneous beat until a particular phase relation is established. The position is perhaps comparable with that of the auricle stimulated electrically at a rate so close to that of the pace-maker that the beats sometimes come from the extrinsic or sometimes from the intrinsic focus.

Whatever the explanation of this may be, there is no doubt that when once the 10 a second flicker rhythm is established it can resist disturbing influences which would upset the spontaneous beat. The central part of the field need not be uniform—the subject can look at a black cross drawn in the centre of the opal screen, seeing its outlines clearly, and he can solve problems in mental arithmetic which would certainly abolish the Berger rhythm. To some extent this is true of the flicker response in general, but at the higher rates pattern vision, &c., usually causes some reduction in the size of the waves. The greater stability of the flicker response is natural enough: with flicker a co-ordinated beat is imposed on the area by the rhythmic excitation, whereas with the spontaneous waves there is nothing but their own interaction to synchronize the different neurones.

It is perhaps remarkable that the area can be excited rhythmically by the flicker, when it seems to be unaffected by a single change in the degree of illumination in the field. It would be easier to explain the cortical mechanism if a steady bright field gave a faster rhythm than a dark field, as it does with the response of the optic ganglion (cf. fig. 12), but the fact remains that the rate can never be altered by changing the light intensity unless the changes are repeated very rapidly. Apparently the area is not concerned with the perception of light, but is near enough to the striate region to be affected by a rhythmic pulsation there.

DISCUSSION.

If the Berger rhythm represents a spontaneous beat of a group of neurones, it is not surprising that the frequency is much the same in all individuals and under all conditions. Unless a different rhythm is imposed by flicker the synchronized beat can only occur when the

neurones are undisturbed; the rate of beating will then depend on the constitution of the cells and on nothing else. Thus the Berger rhythm is disappointingly constant, for it expresses time relations which are determined by the fundamental properties of the cells.

Berger has investigated the rhythm in a very large number of subjects in different conditions, e.g. sleep, anæsthesia, drug intoxication, &c., and has reported certain instances of a slow rate associated with pathological states of the brain, but in normal subjects the rate is seldom less than 9.5 or greater than 10.5 a second. There are, however, considerable variations between one subject and another in regard to the persistence of the rhythm and the fluctuation in the size of the waves. One of us (E.D.A.) gives the rhythm as soon as the eyes are closed, and maintains it with rare and brief intermissions as long as they remain closed. The other (B.H.C.M.) is better in the role of observer than of subject, for in him the rhythm may not appear at all at the beginning of an examination, and seldom persists for long without intermission. In another subject an extremely uniform series of waves appear suddenly 10 seconds or more after the eyes are closed, the record giving the impression that the beat is harder to achieve but more perfectly synchronized when once it has developed. There are also considerable variations between individuals in the ease with which the flicker response can be obtained, in the tendency to give waves at half the flicker rate, in the amount of pattern which can be tolerated in the visual field, &c.

There is no evident connection between these features and any of the known physical or mental traits of the different individuals, but we have not been specially concerned to detect any correlation, since our main problem has been the neural mechanism of the rhythm. Our explanation of it differs considerably from that given by Berger and until its nature is agreed upon the study of individual differences cannot lead very far. If we have not misunderstood his writings, Berger's view of the rhythm is that it represents the normal activity of every part of the cortex; afferent stimuli which claim the subject's attention will cause a more intense local pulsation, but will inhibit the beat over the rest of the brain, with the result that the waves can no longer be detected outside the skull, and visual stimuli are particularly effective in inhibiting the beat since vision plays the most important part in controlling the work of the brain. The evidence of localization and the rhythms induced by flicker seem to us to be definitely opposed to this view. It is possible, however, that the disappearance of the rhythm is sometimes due to

inhibition rather than to the change from synchronous to asynchronous action. Both processes would suppress the beat and our only reason for preferring the latter is that it operates in other examples of nervous rhythm which have at least a superficial resemblance to the Berger phenomenon.

The resemblance to the beat of the retina or of the optic ganglion of insects would have been overwhelming if it had turned out that the Berger rhythm originated in the striate area. As it is, the absence of an "on" and "off" effect and perhaps also the failure to alter the frequency by changing the illumination of the field show that the rhythm is not strictly comparable to that of a pure receptor mechanism like the retina. The suppression of the rhythm by trying to see in the dark is another fact for which there is no certain explanation, though the change from synchronous to asynchronous activity is as likely as any other. But the Berger waves would add very little to our knowledge if everything could be explained so simply. Their greatest interest lies in their relation to the organized activities of the cerebrum. Berger has stressed the importance of the rhythm as a possible clue to the neural mechanism of attention and our failure to agree with his view of its origin does not lessen its interest in this respect.

It is true that, in our view, the rhythm shows the negative rather than the positive side of cerebral activity, it shows what happens in an area of cortex which has nothing to do, and it disappears as soon as the area resumes its normal work. This is almost inevitable, for to give potential waves which can be detected through the skull a considerable area must beat synchronously and it is unlikely that this could occur in any region which was taking an active part in coördinating incoming and outgoing messages. The rhythms induced by flicker represent a positive activity, but one which cannot often occur normally. It is unlikely, therefore, that records made with the skull intact will give detailed evidence of the normal positive activity of different regions of the brain. The Berger rhythm shows the background of spontaneous discharge, but it can also show when that background is obscured and this may be information well worth having, from the practical as well as the theoretical aspect.

SUMMARY.

The paper deals with Berger's discovery that regular potential oscillations at 10 a second can be detected in the human subject by electrodes applied to the scalp. Berger's conclusion, that the waves are

due to the electrical activity of the cortex, is confirmed, but evidence is given to show that they arise from an area in the occipital lobes connected with vision, and not from the whole cortex. The distribution of current in the scalp indicates that the focus of maximum activity, though confined to the occipital region, can change its position from time to time.

The essential condition for the appearance of the Berger rhythm is that pattern vision should be absent. It develops when the eyes are closed or if the visual field is uniform, and disappears whenever the central part of the field has any detail. The attempt to see detail, even though the field is uniform, abolishes the waves: for this reason the closure of the eyes, by withdrawing the attention from visual phenomena, aids the development of the rhythm. Its frequency is not altered by changing the illumination of the field, and it is not abolished by the perception of light and darkness or by visual imagery. In patients who have been blind for some years we have not been able to detect any trace of the rhythm. As Berger has shown, non-visual activities which demand the entire attention (e.g. mental arithmetic) abolish the waves; sensory stimuli which demand attention do so too.

We believe that the potential waves are due to the spontaneous beat of an area in the occipital cortex which is normally occupied by activities connected with pattern vision. When the area is unoccupied the neurones discharge spontaneously at a fixed rate (as in other parts of the central nervous system) and tend to beat in unison. Visual activity and widespread non-visual activity break up the synchronous beat by exposing the area to non-uniform excitation. In man a large area is normally occupied with visual activities; thus when the area has nothing to do and is free to develop a synchronous beat the potential changes are large enough to be detected outside the skull. It appears that the area does not remain permanently unoccupied if vision is lost; in subjects who are blind it must have become more accessible to the rest of the brain.

The close relation of the area to the visual mechanism is confirmed by the fact that the frequency of the rhythm can be altered by exposing the eyes to a uniform field which flickers at varying rates. The waves then tend to occur with the same frequency as the flicker. The frequency of the spontaneous rhythm varies within narrow limits in different subjects, but there is much individual variation in the persistence of the rhythm, uniformity of the waves, &c.

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SPINAL SHOCK AND SOME FEATURES IN ISOLATION- ALTERATION OF THE SPINAL CORD IN CATS.

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THE experiments to be described supplement observations made by Ballif, Fulton and Liddell [1], who found, after acute total section of the spinal cord in cats, a long, lasting susceptibility of the knee-jerk to inhibition produced by a single break shock. In the present series their observations are repeated some time, days or weeks, after total section of the cord.

INTRODUCTION.

The word "shock," as applied to the nervous system, was frequently used by Marshall Hall [16]. In his "New Memoir on the Nervous System," 1843, p. 30, there occurs the following passage: "*Immediately* after decapitation, or the sudden amputation of a limb, a diminished condition of the reflex excito-motor power is observed. I divided the spinal marrow in a frog; the reflex actions ceased; in a few minutes they reappeared, and in a short time they were perfectly restored: I remember the late Captain Kater relating an experiment in which the legs of the *Tipula* (long-legs) were removed by means of a pair of scissors, successively, without any manifestation of pain, or impression of any kind; it was placed under the influence of shock." W. Cruikshank, 1795, had observed that, in the dog, division of the spinal cord in the neck was followed by muscular relaxation in the legs [5]. Marshall Hall, on p. 34 of his book continues: ". . . after division of the spinal marrow, the animal is placed under the influence of *shock* and the excito-motor power with the reflex actions are suspended for a time. After a short interval, however, this power with its phenomena return: the limbs stretched out are then stimulated by its firm pressure against the table, and an excited action with the retraction of these limbs occurs." Nine years later, in the "Synopsis of the Diastaltic Nervous System," 1852 [10], the narrower definition of shock is reaffirmed (p. 70). "If we take a frog and divide the spinal marrow near the cranium, the animal is affected by *shock*: the diastaltic force is

suspended, there are no diastaltic actions, or only such as are very feeble. In a few minutes the diastaltic power and phenomena are restored, the effect of shock having passed away."

Thus the term "spinal shock" has come to denote the cessation of movement in the extremities after transection or gross injury of the spinal cord. The degree of cessation of movement is variable, depending in part on the position of the subject in the animal scale, and pertaining, as is now well known, only to the direction aboral from the lesion [31]. In the cat and dog, the majority of reflexes return only after some hours or days, as a rule, and in the monkey much later, if at all [31], depending on the species [13].

Although the word "shock" is often used to connote the deportment of the subject for the whole of the remainder of its existence after section of the spinal neuraxis, it seems preferable that the status should be divided into two stages: (1) that of shock, enduring only for a few hours or days after the lesion, (2) that of isolation-alteration (Munk's Isolations—Änderung [28]), a stage of amelioration and increased excitability ensuing in some species of animals after shock, during which the diastaltic and simple reflex movements reappear. In other species, e.g. some monkeys, muscular dystrophy and nutritional regression are severe, and mask or counter amelioration of the nervous system [12, 23]. Isolation-alteration varies according to the species of animal.

As to the nature of shock itself, Goltz's view [14] is now discounted, since it is difficult to conceive of such long-continued abrogation of movement as being due to inhibition, which is an active process, and, as such, demands a seat of origin. Monakow [27], on the other hand, ascribed the absence of movement in the early stages after the lesion to diaschisis, a state in which, as he believed, there was passive abolition of excitation at synapses. Sherrington, too, has preferred to regard shock as a deficiency phenomenon [31, 32], in which the lower centres are deprived of what were later described by Pike [30] as "tonus impulses" from higher centres. There is evidence that "loosening of the nexus" between higher and spinal centres leads to deficient excitability [32]. The present experiments are interpreted in substantiation of that view.

"Shock does not at longest persist for more than a few days." The centres adjust themselves to the lack of excitation, so that shock passes off and the subject attains the second stage in the status of spinalinity. In this stage, that of isolation-alteration, examination of the subject becomes more feasible. During shock, the irresponsive background implied by the very name is, in the main, characteristically intangible.

As shock passes off, the first few reflexes elicited are of the simplest. As the stage of isolation-alteration progressively emerges, a larger number becomes available for examination. In the cat, the knee-jerk and ipsilateral flexor reflex [15] suffer but briefly from the shock of spinal section and are often elicitable immediately after it [11]. The crossed extensor response begins to appear somewhat later [22, 26]. After two or three days fibrillary movements begin in the muscles. At their onset in the cat, these movements are irregular and tremulous, of small excursion, but later they become larger and show a tendency to develop into stepping. They occur spontaneously when the animal is held up for examination and are affected by an external stimulus such as pinching the tail. These movements form a constant accompaniment of events in isolation-alteration. Their cause and origin are unknown. Apart from lack of neural excitation from higher centres, there has, of course, been infliction of injury to the nutritional system of part of the cord, both as regards blood supply and flow of cerebrospinal fluid.

With new knowledge of spinal function, ampler speculation seems justified as to the nature of shock and to the course of events in isolation-alteration. The factor of importance is the nature of the liaison between the terminal branches of an afferent nerve and those functional aggregations of motoneurons which comprise the motor centre (motoneurone pool). The agents of liaison which transmit excitation (or inhibition) to a neurone are believed to be the *boutons terminaux* at the neurone's surface, both on its perikaryon and its dendrites [2, 18, 19]. The mechanism of excitation is believed to be concerned with the generation of a point of depolarization (central excitatory state, *c.e.s.*) on the neurone's surface underneath each bouton. The area of surface in apposition to a bouton is the "synapse," whose activities form the characteristics of central nervous action.

The number of boutons, and hence of synapses, in application to a single perikaryon in the ventral horn is 300 to 350 (cat) [19]. On such a final motoneurone are boutons that have taken origin from widely different sources, being transmitters of excitation, through relay cells, from numerous reflex fields such as areas of skin, or a neighbouring muscle or group of muscles, or from the selfsame muscle which is innervated by the final motoneurone in question. A proportion of boutons represent the end of a relay, whereby impulses from the

¹ After many anaesthetics, the crossed extensor responses may not appear for two to three days. Dr. G. P. McCouch, of the University of Pennsylvania, informs me that he obtains that reflex twenty to thirty minutes after transection under divinyl ether.

cortex, mid-brain, vestibule and other supraspinal sources arrive at the final motoneurone.

Within a motoneurone pool (motor centre) a single afferent nerve-fibre is known to excite different neurones of the pool to different intensities. Another afferent nerve-fibre will excite its own group of neurones to different extents also. At the periphery of the field of each nerve-fibre's influence, there lie neurones which are within the fringe of excitation of each, but are excited only to a subliminal intensity. Such neurones, however, may lie within the fringes of two contiguous fields so that when two afferent nerves or two nerve fibres of different provenance are excited simultaneously, the neurones are excited liminally and discharge [8, 33, 34].

According to this conception, the boutons subserve the function of linking the neurone with distant organs, the intensity of representation of any source being probably related to the number of boutons, at least in part. The perikaryon or some part of it discharges in response to conditions which, at first sight, might seem at variance with the behaviour implied by the term "all or nothing." This variance documents itself as a reluctance to discharge in response to a single stimulus from a single afferent nerve (1) if only a few afferent nerve-fibres, and therefore boutons, are in action; (2) if the activity of the boutons is infrequent.¹ In either case, the variance is due to the summing of central excitatory processes at the synapses failing to reach neurone threshold required for discharge. No discharge, therefore, occurs and the central excitatory state diminishes to its resting value. In other words, areas of depolarization under the boutons, in the one case, are too dispersed and in the other case, too tenuous to reach the threshold value which surface-depolarization as a whole must reach before discharge is initiated. On the contrary, when an adequate number of boutons receive impulses in sufficient frequency, depolarization of the motoneurone and its discharge ensue. Thus motoneurones, and indeed all neurones, are played upon by variously sized bunches of boutons terminaux connected with different sources. Their discharge, once initiated and transmitted to the axon, are new-born nerve impulses.

After the discharge, depolarization of the surface subsides and repolarization follows. When the motoneurone is not discharging, or

¹ It is an established experimental fact that peripheral nerve is sensitized to subsequent stimulation by a preceding subthreshold stimulus which, by itself, is ineffective. (Gildemeister phenomenon) [10].

has not just discharged, but is at rest, there exists on its surface dispersed points of depolarization forming an unstable background of maculate excitations, which, though summed, have a subthreshold value for exciting the neurone as a whole. The neurone at rest, therefore, is kept on the *qui vive*, so that when a fresh accession of stimulation from a new source, as in a fringe [8], is adequate to raise the surface depolarization to threshold value, there is less leeway to make up because the effectiveness of the new stimulus has been facilitated by the pre-existing state of subliminal excitation on the surface. Besides excitatory boutons, there are some boutons which have the property of inhibiting surface change (central inhibitory state) and of preventing or showing discharge thereby.¹

Thus the final motoneurone which controls skeletal muscle, or the relay neurone above it, is played upon by boutons of widely different provenance. Each source of excitation (or inhibition) casts its fringe upon the pool of motoneurons. Hence it comes about that when the spinal cord is transected in part or whole, the lesion stops the normal torrent of impulses from higher centres, fringe effects are reduced, and the background of subthreshold excitation diminishes. The subnormally small streams of excitation from lower (spinal) centres and from the muscle itself then sum only to a subnormally low grade of subliminal value; the motoneurone is excited much less easily because subnormally less on the *qui vive* and the muscles become almost or entirely flaccid. This is "spinal shock," or diaschisis, the passive withdrawal of excitation. Although the distribution of afferent nerves (convergence) has an anatomical framework, that framework is only useful for conveying impulses when vivified by a healthy state of functioning. Fatigue or failure of blood supply reduces the field for the time being. With spinal shock the reduction is more permanent, but recovery soon begins to show itself, at least in the cat, and the fractions within the pool may be larger at three hours than at two hours after transection [4]. Strychnine increases the fraction, anæsthetics diminish it. Ephedrine increases the reflex excitability of spinal monkeys [21]. In cats, the crossed extensor reflex disappears on section, but, as already mentioned (p. 388), soon shows recovery. In the dog the stretch reflex disappears after spinal section, but reappears in fractional form after some days [6]. Some years ago, in unpublished observations with J. F. Fulton, evidence

¹ Dr. McCouch kindly informs me that for flexor muscles the effectiveness of inhibitory stimuli from the contralateral side is impaired after spinal transection, but recovers after a time.

was found to suggest the continuance of the stretch reflex in cats for a few seconds (ten to twenty) after spinal transection. McCouch and Fulton [25], by withdrawing excitation fringes in two stages, have produced shock in two stages. Their method was to extirpate a limb-area from the motor cortex on one side. The limb affected by that operation was given time to recover somewhat, and then the spinal cord was transected above the level of the limb's supply. The limb, deprived of excitation for a second time, showed shock again, but to a less extent than the fellow limb, which now suffered shock for the first time, and that completely.

In the early stages of isolation-alteration, therefore, as it emerges after shock, the neurone is less on the *qui vive*, and can be roused only by strong stimuli, i.e. stimuli which activate many boutons. Such stimuli are effective in the cat or dog, for instance, only when they represent nociceptive stimulation of a limb or phasic stretch reflexes (knee-jerks), but not static (postural) stretch reflexes, since in the latter the stimuli are too asynchronous or too infrequent to elicit discharge [6, 12]. In the monkey, although there is great difference between species and individuals, deprivation of background excitation is so severe that a knee-jerk is not elicitable, at least for some hours (*Erythrocebus patas*) or days (*Lasiopyga roloway*) [13]. In the cat or dog, the lack of background excitation has been less severe [31]. Often a higher resting tension must be imposed upon the knee-extensor before the jerk can be elicited, that is to say, the reflex centres are now more dependent for excitation (central excitatory state) upon the muscle itself. This feature decreases with the passage of time (p. 398), but nevertheless seems to persist indefinitely in some degree. Another feature is the irregularity of response in a series of knee-jerks, which suggests that, owing to lack of background excitation from other sources, the centres have become especially sensitive of excitation derived from the muscles' own tension receptors and more appreciative of small irregularities inevitable in the mechanical tap. This phenomenon also diminishes with the lapse of time subsequent to spinal section. Moreover, in a series of tendon taps, often the first few elicit larger jerks than the later, when a steady state is reached. If the preparation be left one to two minutes, this fatigue disappears and large jerks are again elicitable for a time. This dependance upon background excitation came to notice in another way. At one stage of the investigation, the jerk was elicited by fixing to the myograph the armature of an electromagnet in such a way that the tendon, which, as usual, had to be detached from the tibial

tuberosity, could be slackened slightly when the current excited the electromagnet (Phillips [29]). When the current was broken, the myograph swung towards its zero, and in so doing, subjected the tendon to a sudden lengthening and excited the stretch organs of the muscle. The rate of release of the myograph arm and therefore the rate of lengthening of the muscle was controlled electromagnetically by a pendulum which moved a slide along a resistance, so that the rate was variable. Since the mechanical pull on the muscle did not alter in direction, as it might do slightly when the tendon was tapped by hand, it was ensured that the same fractions of the muscle were stimulated on each occasion. It had been hoped to use this device for eliciting the knee-jerk during the investigation. It had to be discarded, however, because it failed to elicit a jerk in the early days after transection, even when the muscle was lengthened slowly. Its failure in the acute spinal state was due to the fact that the preliminary slackening of the muscle reduced background excitation in the nerve-centres to a low value, with the result that when the stretch was given to the muscular organs, even slowly, the central excitatory state derived therefrom did not build up to threshold value, and consequently no jerk was elicited. On the other hand, with an ordinary decerebrate preparation, because of its ample margin of background excitation, the mechanism was uniformly successful in eliciting responses, as it was also in a spinal preparation when some degree of recovery had taken place, although no sign of postural stretch reflex might yet be present. In spite of its being put aside during the present research, the device carried promise as a means of assaying background excitation. Dr. McCouch has pointed out that a further reason for its failure, at a time when a hammer tap on the tendon was an adequate stimulus, might be that the hammer succeeds by stimulating also the circumpatellar tissues, and so arouses a further source of excitation [24].

In yet another way, the manner of delivering the tap in spinal preparations is important. A tap given by the index finger to the tendon, when the latter is detached from the tibial tuberosity and hooked up to the myograph, is of longer duration than the tap from a metal rod or hammer. Nevertheless, the height of the jerk is greater with the finger tap, because there is a longer period for central summation derived from longer recruitment of peripheral stretch organs. In one experiment, for instance, a rod gave a tap of total duration 20σ and a maximum tension of 450 grm. The jerk was 450 grm. tension.

The finger, however, with a tap of 200 grm. and duration 35σ elicited a jerk of 600 grm.¹

The character of the fibrillary tremors, seen within the first week after transection, suggests ceaseless synaptic bombardment, or increased excitation or decreased inhibition, or both. The experiments presently to be described are suggestive of increased excitation.

METHOD OF EXPERIMENTS.

The experiments (twenty-six in number) were made on cats at varying intervals up to sixty days after complete section of the cord at or about the level of the last rib.

Well known as a secondary effect of spinal severance and found in the state of isolation-alteration, is atrophy of muscles, accompanied by dehydration of fascial tissues, which then form an unyielding web especially in the groin. In the cat, the changes are often more marked than in the dog, but they are variable and sometimes slight. They are mentioned here because, when severe, they may tend to hamper movement of the contractile elements and lessen the height of the jerk. In the cases here reported, however, dehydration of the fascia was minimal and the contractile elements were unrestricted.

Before myographic examination, the animal was anaesthetized with di-ethyl ether and decerebrated at the intercollicular level through a trephine opening in the skull. Immobilization of the limb was secured by appropriate nerve section or tendon resection either during the anaesthetic before, or soon after decerebration. The preparation was then left from one to one and a half hours to rest. The myograph was of the reflecting mirror type, with high vibration frequency. The tendon was tapped with a rubber-covered metal rod, or with the index finger. The increase in distance of the animal table below the myograph, and hence the increase in length of the muscle, obtained by lowering the table, was measured with a micrometer gauge.

ACUTE EXPERIMENTS.

As Ballif, Fulton and Liddell [1] showed in the decerebrate cat immediately after spinal transection, a single inhibitory break shock applied to the sciatic nerve lowers the central excitatory state to such a degree that for 200σ the jerk is in complete abeyance. Thereafter,

¹ A criticism which may be levelled against rapid stimulation of stretch organs, and is as yet unanswered, is that rapid extension, because potentially noiceptive, may stimulate the muscle's noiceptors as well as its excitors.

gradual recovery ensues for one or more seconds, until it is complete. Far different from this was the very brief period of abeyance before transection, under 10σ (figs. 1 and 2). Other factors have to be noted after transection, such as an increase in length and resting tension of the muscle in order to raise the subliminal background of synaptic excitation. Rarely, there is a noteworthy departure from this rule. First, the muscle of a very rigid preparation may give such a pronounced lengthening reaction, itself an inhibitory process, and extend so readily that it responds only by a very small jerk, and that after considerable extension. Spinal section appears to impair the lengthening reaction

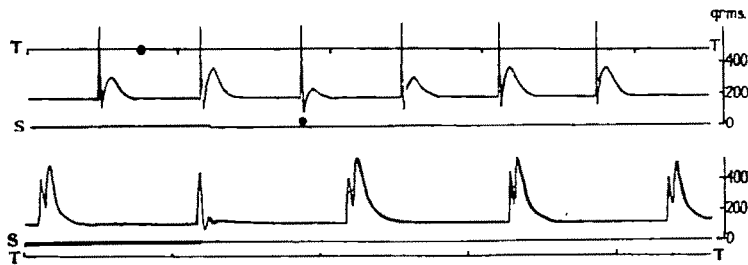


FIG. 1.—A series of knee-jerks, recorded isometrically, forty minutes after complete section of the cord headward of the first cervical vertebra, in a decerebrate cat, without anaesthetic. Fall of signal S shows incidence of single inhibitory break shock applied to ipsilateral sciatic nerve. Two jerks are partly inhibited, the first one more than the second. Recovery is complete in some 2 secs. $T = 1.0$ sec. Tension scale in grm. Artificial respiration.

FIG. 2.—Same preparation, before cord section. One jerk only is inhibited; the one that almost coincides with the inhibitory stimulus. Faster plate than in fig. 1. $T = 0.6$ sec. S, as in fig. 1. Recovery from inhibition is here complete in 0.6 sec., but from other records not reproduced in which the taps were differently timed, it was found to be complete after only 6 σ .

and thereafter the muscle may need to be extended less, even though spinal, to give a jerk. When the inhibitory effect of the lengthening reaction is not so marked as to diminish excitation, increase in length of the muscle (and increased tension) increases the background central excitatory state and increases resistance to inhibition. The increase, however, is more in the nature of a shift of the whole curve from the base line. In spinal preparations, after the lapse of shock, the shift is especially marked and there is then no lengthening reaction to inhibit and reduce the central excitatory state. Another factor increasing synaptic excitation is general vascular impairment, e.g. a failing heart [7, 20]. Except in extreme cases of failure, there is no *prima facie* rise of muscle tension, but the increase in subliminal excitation is considerable, as indicated by the increased height of the knee-jerk and increased resistance to inhibition.

It is convenient to mention here an interesting effect on the lumbar centres when the cord is transected at high cervical level, confirming Harmon and Fulton [17]. The resistance to inhibition is then slightly but distinctly greater than when section is made subsequently at the level of the last rib (fig. 3). This greater resistance is probably due to a measure of excitation derived from the higher spinal centres. That the greater resistance is due to vascular impairment is definitely excluded by the knowledge that a high cervical section causes a greater fall of

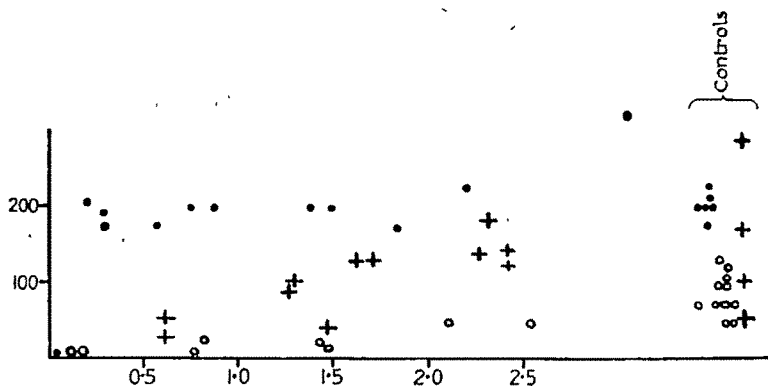


FIG. 3.—Recovery graph of the knee-jerk after inhibition, made from myograph records. Ordinates, tension of jerk in grm. Abscissae, lapse of time in seconds after single inhibitory break shock to ipsilateral sciatic nerve. Control (uninhibited) jerks are shown on extreme right.

• = jerks in decerebrate state, spinal cord intact.

+ = jerks after transection of cord headward of first cervical vertebra: artificial respiration.

O = jerks after transection of cord at level of last rib.

In the decerebrate preparation, recovery from inhibition is rapidly complete, after high spinal section it is slower, after low spinal section it is barely complete after 2.5 sec. Note that the controls are more uniform in the decerebrate than in the spinal states.

Resting length of muscle 11.6 cm.

Additional extension for •, 0.43 cm. = resting tension 75 grm., tap 875 grm.

" " +, 0.53 cm. = " " 112 " " 875 "

" " O, 0.55 cm. = " " 125 " " 750 "

general blood-pressure than a low thoracic section. Munk, without using any specific test, noticed that the reflex excitability of the cord is greater with high than low thoracic section [28]. It is to be noted, from the data appended to fig. 3, that with the descending sections of the cord, there is an increasing need for a greater tension in the muscle to get a fairly steady response, as well as need for a tap of greater amplitude.

CHRONIC EXPERIMENTS.

The operation of spinal transection was performed with full aseptic precautions. Nembutal (40 mgm. per kg. intraperitoneally) was the

customary anæsthetic. The level of transection was about that of the last rib. After operation, nursing care involved attention to regular evacuation of the bladder by manual compression. In such a preparation, subjected to the routine myographic examination after decerebration, it is found, even a week or two after spinal transection, that the

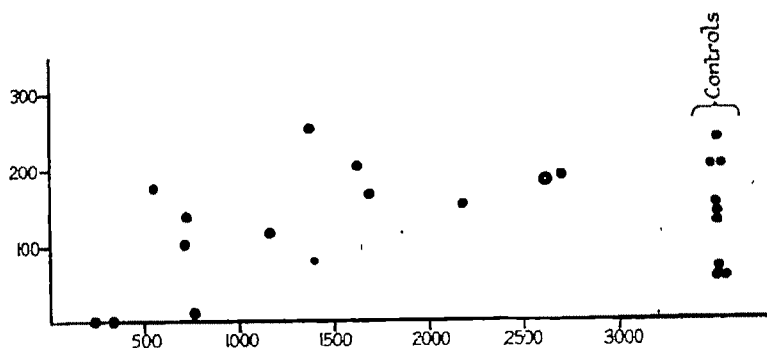


FIG. 4.—Recovery curve four days after severance of cord at 12th thoracic segment. Inhibition of the knee-jerk is complete for 0.8 sec. or more, and thereafter grows less for the next second when recovery is established. Note the irregularity of the control jerks.

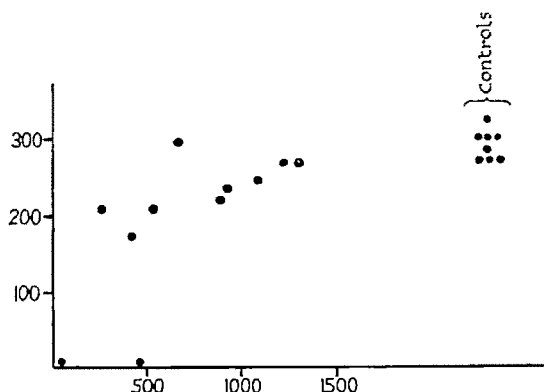


FIG. 5.—Recovery curve twenty-nine days after cord section at 11th thoracic segment. The control jerks are more regular than in fig. 4.

jerks have become much more regular than they are in the acute preparation. Among cases taken as early as the fourth day after transection, increased resistance to inhibition is already established (fig. 4). This resistance gradually gains ground until after twenty days or more the inhibitory break shock is completely effective only for the first 100 to 200σ, after which there sets in a return to normal resistance. The shape

of the recovery curve in such cases bears a close resemblance to that of many decerebrate preparations (fig. 5). In cases of long standing (fifty to sixty days), it is to be noted that recovery after the inhibition is rapidly established (fig. 6) and that when the nutritional impairment of the tissues is slight, the excursion of the jerk exceeds that found in the average decerebrate preparation partly because the shortening reaction is in abeyance. This feature agrees with the free pendular jerk seen

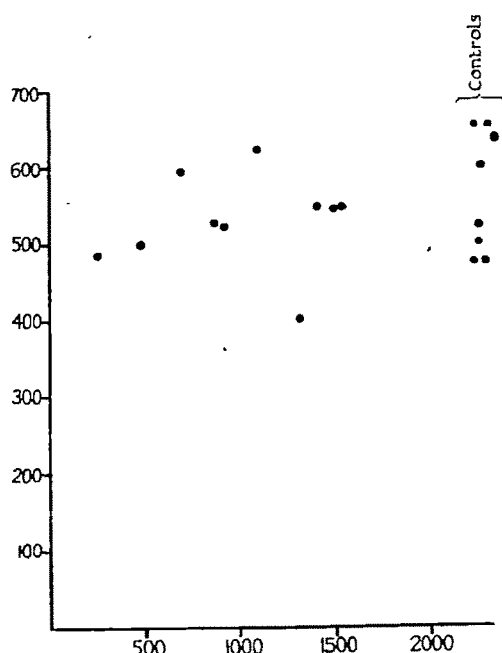


FIG. 6.—Recovery curve fifty-five days after severance at 11th thoracic segment. Complete inhibition lasts for 0.1 sec., and recovery is rapid. The jerks are large and the controls somewhat scattered. Scattering in this case is not due to special sensitivity to irregularities in the mechanical tap, as in fig. 4, which preparation gave jerks only with difficulty. Here the jerks are very easily elicited and their irregularity, though not great in relation to their size, points to lack of autogenetic control from the nerve-endings in the muscle. Similar irregularity obtains also after partial lesions (antero-lateral) of several weeks' standing.

before detachment of the patellar tendon. Eccles and Sherrington [9] have noted that in the chronic spinal dog of eight months' duration, the reflex discharge is much longer lasting than in the acute preparation. Another factor which may also play a part is the well-known effect of the increase of muscle fibre length upon the tension of contraction. The true fibre length, however, is difficult to assess in a partly dystrophic muscle.

The progressive increase of resistance to inhibition, as figs. 4 to 6

show, is a constant feature of the state of isolation-alteration which emerges after spinal shock. It does not appear to be due to decreased effectiveness of the inhibitory break shock, as from degeneration of nerve paths, because repetition of the break shock, two or three times in rapid sequence, inhibits the jerk entirely for several seconds, just as it does in the decerebrate preparation without spinal transection. Nor is there any evidence to suggest that the inhibitory fibres in the sciatic nerve are more involved in degeneration than the fibres in the motor nerve.¹

Another aspect of recovery in the spinal centres is their diminished dependence upon the stretch organs of the muscle to supply a background of excitation. Other sources appear to have become operative to supply the subliminal excitation which normally keeps the neurones on the *qui vive*, and the muscle needs to be stretched less to give regular responses, the tendon taps also need to be less heavy, and this in a muscle in which there has probably been some relative increase of non-contractile at the expense of contractile elements. The following table shows the progressive characters of the change.

Time since section of the cord at approximately the level of the last rib	Length of muscle at rest	Resting extension needed to give regular responses	Maximum tension of tap (gram.)
2 hours	11.6 cm.	0.55 cm.	750
4 days	10.8 "	0.89 "	400
29 "	10.5 "	0.6 "	400
55 "	10.8 "	0.55 "	150

Part of the above data is derived from the same preparations as figs. 4 to 6.

When the cord itself behind the translesion is examined in microscopic section, severe and universal degeneration of perikarya is found in all regions except in the ventral horn. There the number of chromatolysed cells is small. The large majority of ventral horn cells, stained with toluidin blue, appear absolutely normal, even forty days after cord section. In all preparations, the neuroglia appeared normal.

No conclusion, therefore, as to the origin of the increased resistance to inhibition in isolation-alteration is forthcoming from the present investigation.

SUMMARY.

The susceptibility of the knee-jerk of cats to single-shock inhibition has been investigated at various periods after complete section of the cord in the thoraco-lumbar region.

¹ In monkeys, degeneration of the sciatic trunk has been noted, probably because of the sitting posture adopted by the animal, which leads to pressure on the trunk [3].

Susceptibility to inhibition becomes progressively less, until, after fifty to sixty days, the recovery curve resembles that of a decerebrate preparation with the spinal cord intact.

Collateral evidence, derived from the degree of muscular extension needed to produce a given background of excitability, suggests restitution of central excitatory state to almost normal values in the spinal centres. Even if real, such values for central excitatory state are, *per se*, useless to the organism because the nexus with, and command from, higher centres is permanently lost.

The experiments described were begun during a visit of Dr. G. P. McCouch to the Oxford laboratory. I am indebted to him for collaboration then, as well as for continued interest since leaving Oxford.

I have to thank the Christopher Welch Trust for defraying photographic expenses, and Mr. T. Marsland for histological work.

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CONGENITAL DERMAL SINUSES: A SOURCE OF SPINAL MENINGEAL INFECTION AND SUBDURAL ABSCESSSES.¹

BY A. EARL WALKER, M.D., AND PAUL C. BUOY, M.D.

CONGENITAL DERMAL SINUSES.

SACRAL and coccygeal pilonidal cysts or sinuses are common congenital anomalies, but they rarely extend to involve the meninges or the spinal cord. In higher spinal segments, however, sinuses, histologically identical with those occurring in the sacral and coccygeal regions, are found reaching and even penetrating the dura mater. Such congenital malformations, forming an epithelial tube from the skin of the back to the coverings of the spinal cord, are a potential pathway for infection of the subdural and subarachnoid spaces. This source of meningeal infection has been almost completely overlooked in medical literature, and yet once recognized and the condition looked for such a mode of infection is not as rare as might be assumed from the lack of reported cases.

Case 1.—L. I., a girl, aged 5, was referred to the University of Chicago Clinics from the Children's Memorial Hospital, Chicago. From her birth the patient's parents had noted a small dimple in the midline of the upper portion of the child's back. In all other respects the child seemed perfectly normal. At 6 months of age the site of the dimple became swollen, purple in colour and discharged a slightly bloody material. The patient at that time had a high fever and sore throat. Shortly afterwards she began to vomit frequently. A physician noted that the back was rigid and on lumbar puncture found 150 cells in the spinal fluid. After standing for an hour a pellicle formed in the fluid. A portion was injected into a guinea-pig and the animal died three weeks later. Examination of the animal is said to have revealed evidence of tuberculosis. Another observer saw the patient at that time and found her "irritable and cranky." The fontanelle was not bulging; there was no strabismus and no Kernig's sign, but there was definite rigidity of the neck. He thought the child was suffering from an encephalitis. Subsequently another specimen of spinal fluid was injected into a guinea-pig and again the animal died. This was considered conclusive proof that the child was suffering from tuberculous meningitis.

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This illness, with great irritability, evening fever, vomiting, loss of appetite and rigidity of the back, continued with varying degrees of intensity for about eighteen months when, for no apparent reason, the child recovered and remained perfectly well until 5 years of age. During the intervening three years, however, the mother had noticed an occasional discharge from the dimple of a few drops of milky material, which was at times blood stained. This occurred two or three times a year and on two occasions the skin surrounding the dimple became red and swollen.

During November, 1932, the patient began to complain of pain in the neck and back, particularly at night. She was taken to the Children's Memorial Hospital. Examination at that time showed a spasm of the left sternocleidomastoid muscle, a scoliosis of the upper thoracic vertebrae with the convexity to the right and a small, slightly elevated dimple just above the spine of the 5th thoracic vertebra. Both knee and ankle jerks were very lively and a bilateral, sustained ankle clonus was present. The right plantar reflex was extensor and the left flexor. Roentgenograms showed an incomplete fusion of the laminae of the 4th thoracic vertebra and a marked spinal curvature. After ten days in the hospital the patient's condition improved greatly and she was discharged. During the following months she was examined at frequent intervals in the out-patient department of that hospital. Her gait became progressively more spastic, the reflexes of the lower extremities more active, and at times local tenderness was present over the 4th and 5th thoracic vertebrae.

Because of this steady progression of her condition, she was readmitted to the hospital on April 22, 1933, for lumbar puncture. The fluid was clear, under normal pressure, contained three lymphocytes and gave a negative reaction for globulin (Pandy). The Wassermann test on this fluid was negative. She was again treated in the out-patient department. Late in June the patient began to scratch and rub the ulnar surfaces of both hands and arms, presumably as a result of paræsthesiæ. Due to this rubbing, it was noted on her next visit on July 3 that the ulnar surfaces of both forearms were red and inflamed. The findings on neurological examination at that time were essentially as they had been previously. Roentgenograms showed no change in the appearance of the thoracic vertebrae, or of the defect in the 4th vertebra. A lumbar puncture revealed a xanthochromic fluid under very low pressure, containing fifty red blood corpuscles and an increased quantity of globulin as tested by Pandy's method. Queckenstedt's test revealed a partial block in the spinal subarachnoid space.

On July 18, 1933, she was admitted to Bobs Roberts Hospital of the University of Chicago Clinics for an exploratory laminectomy. However, she shortly developed measles, thus delaying the operation. On August 10, 1933, examination revealed the dimple previously noted just above the spine of the 5th thoracic vertebra. This was not tender, seemed freely movable on the underlying tissues and no discharge could be expressed from it. Neurological examination revealed no abnormality of any of the cranial nerves. The tendon reflexes of the upper extremity were normal; those of the lower very brisk

the right somewhat more so than the left. A sustained ankle clonus was present on the right side and a transient clonus on the left. The right abdominal reflexes were sluggish, the left brisk. Both plantar reflexes were extensor in type. No definite sensory level could be found, although at times one gained the impression that sensory perception was not as acute over that portion of the body below the upper thoracic region. The finer modalities of sensation (two point discrimination, position-sense, stereognosis, &c.) could not be tested owing to the patient's failure to co-operate. There was no localized atrophy in any muscle group, but in general the strength was poor. No increased resistance was encountered on passive movement of the upper extremities, but in the lower extremities there was definite extensor rigidity, which was more marked on the right side. Co-ordination was fairly good throughout. A scoliosis with its convexity to the right in the upper thoracic region and a compensatory curve in the lower thoracic and upper lumbar region were present. The gait was spastic and the patient walked with small, uncertain steps. When standing with her feet together and the eyes open she did not sway, but on closing her eyes she tended to fall to one or other side.

A lumbar puncture at this time showed clear cerebrospinal fluid under a pressure of 110 mm. of fluid. Jugular compression (bilateral) caused a slow rise to 240 mm. and an equally slow return to 110 after release of the pressure, indicating a partial block of the subarachnoid space. Removal of 3 c.c. of fluid caused the pressure to fall to 80 mm. No cells were found in the fluid and the total protein content was 64 mgm. per 100 c.c. Roentgenograms revealed the defective closure of the laminae of the 4th thoracic vertebra previously mentioned.

On August 16, 1933, under ether anaesthesia, a laminectomy of the 3rd, 4th and 5th thoracic vertebrae was performed. The spine of the 4th thoracic vertebra was absent and the imperfect closure of the posterior neural arch which had been observed in the roentgenograms was seen. The dimple was found to be continuous with a tough stalk of tissue about 3 mm. in diameter. This stalk contained a minute central canal from which thick caseous material could be expressed. The stalk extended from the dimple downward through the posterior spinal muscles, through the defect in the laminae of the 4th thoracic vertebra to the dura mater, to which it was firmly attached. Beneath the dura mater at this point a firm mass was palpable. The dura mater above the tumour mass pulsated normally, but no pulsation was present below it. The dura mater was incised around the fibrous mass, exposing a thickened, white, and opaque arachnoid membrane. The arachnoid membrane about the margins of the tumour fused with the greatly thickened dura mater, and both were incorporated in the thick fibrous mass which was firmly adherent to the posterior surface of the spinal cord (fig. 1). This mass could be removed only by cutting it off the posterior surface of the spinal cord. This procedure revealed within the mass numerous cystic spaces containing a thick caseous material which on examination was found to contain many pus cells, but to be sterile on culture. After

removal of the fibrous mass palpation disclosed that the entire spinal cord was exceedingly firm at this level for a distance of 1.5 to 2 cm. Laterally, the spinal cord was firmly adherent to the much thickened arachnoid and dura mater, but no additional masses or abscesses were found. The dura mater was closed above the site from which the tumour mass had been removed, but closure at that point was not possible because of the large dural defect. The closure of the wound was made in the usual manner except that a small soft rubber drain was left in place.

The post-operative course was uneventful. Except for a moderate amount of pain at the operative site, the patient made no complaint. Both sensation and movement in the lower extremities remained good. Since the cultures of

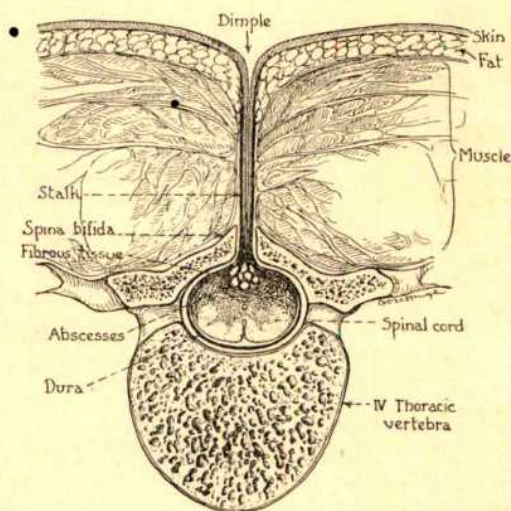


FIG. 1 (Case 1).—Diagrammatic representation of the congenital dermal sinus and the spina bifida of the fourth thoracic vertebra.

the purulent material were negative, the drain was removed on the second day and the wound healed per primam. For the first week she had urinary and faecal incontinence, but then recovered complete control of her bowel, and partial control of micturition.

Neurological examination two weeks after operation showed little change from the findings on admission. An indefinite level of impaired perception of pin-prick was present at the 3rd thoracic dermatome. The reflexes of the lower extremities were still very brisk, with ankle and patellar clonus and bilateral extensor plantar responses. The strength in the lower extremities was fairly good, although at first the patient walked on a wide base with a spastic gait. In Romberg's position she was fairly steady even with the eyes closed.

She was discharged to a convalescent home and when seen six weeks after operation had no subjective complaints. She walked much better, although the

PLATE XIII.

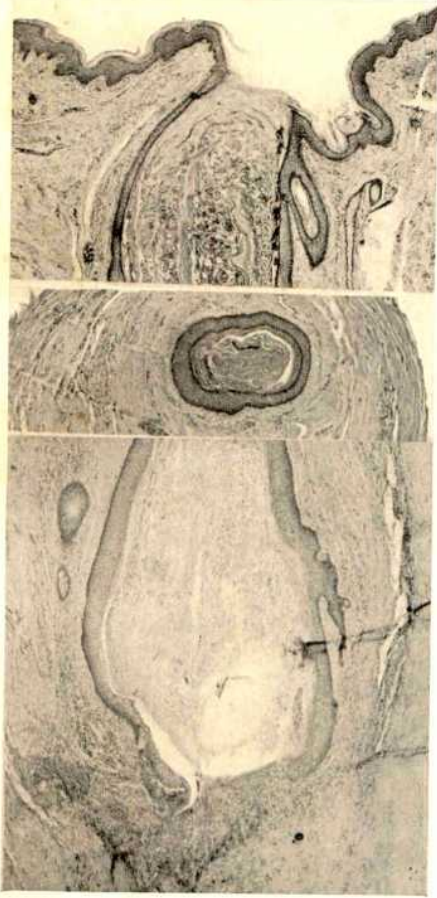


FIG. 2.

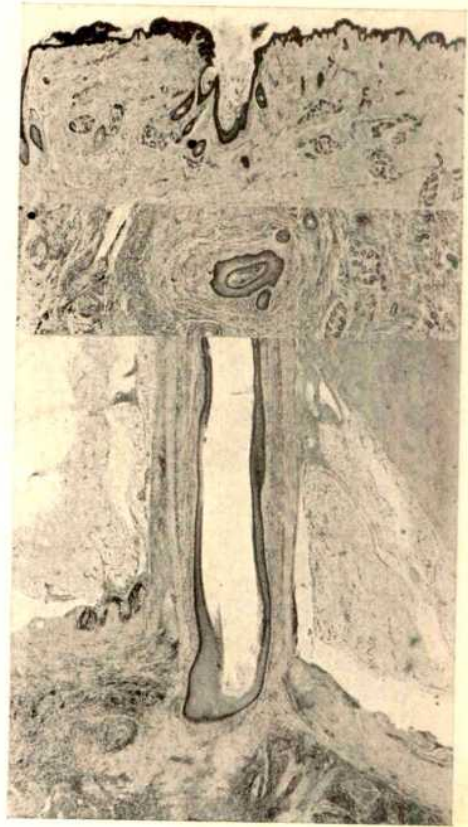


FIG. 4.

FIG. 2 (*Case 1*).—Composite plate of the congenital dermal sinus showing the stoma, the duct and a part of the abscess at the base of the sinus. Hæmatoxylin and eosin.

FIG. 4. (*Case 2*).—Composite plate of the dermal sinus showing the stoma, the epithelial tube, and its ending in an inflammatory mass beneath the dura. Hæmatoxylin and eosin.

gait was still somewhat spastic. She had perfect control over her bladder and bowel. The reflexes of the lower extremities were still quite brisk with ankle clonus and Babinski's sign on both sides.

On December 16, 1933, she was able to walk and run about without any sign of spasticity or limp. The tendon reflexes of the lower extremities were brisk and both plantars were extensor. A sustained ankle clonus was present on the right side. No sensory change could be demonstrated in any part of the body.

The family history is irrelevant except that a maternal cousin of the patient has a tuft of hair and an area of thin skin about 2 cm. in diameter in the upper lumbar region. The patient's father is suffering from schizophrenia of the paranoid type.

Pathological examination (Plate XIII, fig. 2).—The specimen removed at operation consisted of three pieces of tissue. The first was a bit of skin about 3 cm. in diameter, in the middle of the undersurface of which could be seen a round white tube of fibrous tissue with a small central orifice. The second was the stalk connecting the skin with the contents of the spinal canal. The third was a tough fibrous mass of tissue, cylindrical in form, 1.5 to 2 cm. in diameter, one surface of which was covered with dura mater while from the other thick caseous material could be expressed. The tissue was fixed in formalin, embedded in paraffin, and cut in serial sections, at right angles to the skin surface in the case of the first specimen and parallel to the long axis of the subdural mass. Cross sections were made of the stalk.

The sections were stained with hematoxylin and eosin for cellular detail; with van Gieson and Perdrau's method to show connective tissue. Sections from the subdural mass were stained by Loyez's method for myelin.

Study of these sections shows that the malformation consists of a tube of epithelial tissue opening out on to the surface of the skin at the dimple and extending downward to the mass lying beneath the dura mater, which was in turn closely attached to the posterior surface of the spinal cord. The skin about the mouth of the tube shows little change except some subdermal fibrosis. Near the stoma an occasional hair follicle is seen arising from the epithelium of the tube. Deeper, however, no hair follicles or other dermal appendages are present. The stoma itself and the canal of the stalk are lined with stratified squamous epithelium and plugged with desquamated epithelium arranged in concentric layers, in the centre of which is more debris irregularly arranged.

The epithelial lining of the tube becomes thinner as one approaches the inner end. The internal surface is devoid of papillæ and hence smooth. Although the cells of the stratum granulosum are less numerous, granules of keratohyalin are prominent. At the very bottom of the tube the epithelium is defective. Surrounding the tube is a thick layer of collagenous fibres which may be followed to the base of the tube where it is continuous with the thickened dura. Along the epithelial wall of the duct are small collections of lymphocytes and occasionally a calcospherite, both becoming more numerous as the stalk approaches the dura. The epithelial tube, however, terminates above the

dura, about $1\frac{1}{2}$ cm. above the spinal cord, giving way to a mass of fibrous tissue. Beginning immediately below the lower and defective end of the epithelial tube, this fibrous mass becomes densely infiltrated with inflammatory cells, small round cells, plasma cells, macrophages and an occasional polymorphonuclear leucocyte. The dense connective tissue mass is composed largely of thick fibres of collagen, a few fine fibres of reticulin and a few fibroblasts. In many places within this thick felt-work of connective tissue small abscesses are seen containing cells similar to those noted above, and many multinucleated giant cells of the "foreign-body" type. No bacteria were seen in these abscesses and it will be recalled that no organisms could be cultivated from this purulent material. Nowhere is any nervous tissue seen.

Dr. George W. Barthelmez, of our Department of Anatomy, very kindly examined sections of this malformation. He was of the opinion that the histological appearance of the skin in the sinus with a narrow malpighian layer and no papillæ was embryonic in character and resembled that on the dorsal side of the finger tip in a four months' foetus. He considered that the small epithelial proliferations from the skin of the sinus near its base were primordia of sebaceous glands, and comparable to findings in embryonic skin.

In brief, the pathological picture is that of an epithelial tube extending from the skin through unfused spinal laminae to an inflammatory mass composed of numerous small sterile abscesses lying beneath a thickened dura, involving the arachnoid and attached to the posterior surface of the spinal cord. In this case of spina bifida, instead of the usual type of developmental abnormality in which a "firm fibrous band of connective tissue, fat, elastic tissue and striated muscular fibres passes through the vertebral cleft and connects the cord with the overlying skin" (Frazier [2]), the cord was connected by an epithelial tube passing through the defect in the lamina to the skin on the surface of the body.

This congenital malformation is identical with the pilonidal sinuses which occur in the sacral and coccygeal regions. The name pilonidal is a misnomer since only 40 per cent. of those sinuses contain hair (Owen [6]). For that reason we have called these malformations congenital dermal sinuses as we believe this more accurately describes the anatomico-pathological condition. Histologically, however, there is no distinction between the two anomalies.

With an understanding of the pathology of the case it is easy to explain the pathogenesis of the patient's earlier illness, diagnosed as tuberculous meningitis, from which she recovered. In the course of time infectious material undoubtedly found its way into the epithelial tube through the open stoma which appeared as an inoffensive dimple on the surface. This set up an inflammatory reaction within the tube

as is attested by the infection about the dimple and the sanguinous purulent discharge observed by the parents. This infection spread through the end of the tube to the dura, which was one with the connective tissue wall of the tube. The intradural abscess progressively grew, irritating the underlying leptomeninx and thus setting up a sterile meningeal reaction which was diagnosed as a "tuberculous meningitis." This not surprising error was reinforced by the unexplained death of the guinea-pigs.

If now in retrospect we continue the interpretation of this patient's story we must conclude that in the course of several months she overcame the localized infection with the resultant subsidence of the generalized meningeal reaction. She then enjoyed three years of apparent good health, at the end of which time sufficient infectious material again entered the epithelial tube to initiate a second illness. Again, we see evidence of extension of the inflammatory reaction, probably sterile, far beyond the seat of the infection as indicated by the paræsthesiæ of the ulnar surfaces of the fore arms (eighth cervical and first thoracic dermatomes). The proliferative process which succeeded the initial infection during the first years of life had undoubtedly left a thickening of the meninges, to which this second infection now added abscesses and inflammation sufficiently increasing the size of the connective tissue mass to compress the spinal cord. In addition, adherence of the inflammatory mass to the spinal cord produced a reaction within that structure. From both these factors a paraplegia resulted, but the sensory pathways were not affected. This resistance of the sensory fibres to various pathological processes which damage the motor tracts is, of course, a commonly observed phenomenon in many diseases of the spinal cord.

When our findings in this first case were reported to Dr. Joseph Brennemann of the Children's Memorial Hospital, Chicago, he immediately informed us that he had another young patient which he felt sure must be suffering from the same condition. Accordingly the following case was referred to us.

Case 2.—J. S., a 3-year-old white girl, was admitted to the University of Chicago Clinics from the Chicago Children's Memorial Hospital on March 9, 1934, with the complaint of stiffness and pain in the back and progressive weakness in both legs since June of 1933. She was the younger child in a family of two. Her mother had had two miscarriages. Her birth and developmental history were quite normal. A small hairy mole over the fourth lumbar spine had been noted since birth. She had had no illness or operations, but

in February of 1933 she fell from a chair and fractured her left femur, for which she was put in traction for five and a half weeks. During that time she complained occasionally of pain in the back, but it was not noticed until three months later that she had difficulty in walking upstairs and was unable to bend forward. Later, in August, she complained of itching and painful feet, and in September she was admitted to the Children's Memorial Hospital. Blood and urine examinations at that time were normal, the Wassermann and Kahn reactions on the blood were negative, and both Mantoux and Von Pirquet skin tests were negative. Spinal puncture on two occasions showed 700 and 680 cells, 83 and 32 per cent. respectively of which were lymphocytes. Culture of the first grew *B. proteus*, but no growth could be obtained from the second specimen. Tuberculous meningitis was suggested as the most probable diagnosis. Roentgenograms of the heart and chest were normal.

The child was removed from the hospital against the advice of the physicians, but returned because of weakness of the left leg. On January 3, 1934, the patient complained bitterly when the legs or feet were moved, and seemed to have paræsthesiæ in the left foot. Neurological examination showed that all the cranial nerves were normal; knee and ankle jerks on both sides were absent; both plantar reflexes were flexor. There was a marked weakness of the peroneal groups of muscles of the left leg, but the remainder of the muscles of the lower extremity seemed normal. No gross sensory change could be detected. At that time attention had been called to our first case, and the reddened lumbar nævus was then examined with great interest and the correct diagnosis was readily agreed upon.

On account of an outbreak of exanthemata, operation had to be postponed and the child was sent home until the period of quarantine was completed. During that time she seemed quite active and had no complaints until one week before admission to the University of Chicago Clinics, when the left leg became paralysed and the right very weak. Two days later she had incontinence of faeces and retention of urine with overflow incontinence. She had no appetite and was restless and irritable. On several occasions the hairy mole in the lower lumbar region became red and swollen.

Physical examination revealed a pale, poorly-nourished, but fairly well-developed girl of about 3½ years of age lying quietly in bed, her left leg in the posterior half of a cast. She co-operated readily, but was apprehensive. Her general physical examination was negative except for the neurological findings.

The cranial nerves were unaffected and the upper extremities were normal in motor, sensory and reflex muscular status. The abdominal reflexes were absent. There was no movement of the umbilicus when the head was raised. At the first examination, March 12, 1934, both ankle-jerks could be obtained, but four days later both were absent. The knee-jerks were constantly absent. The plantar reflexes were bilaterally flexor. No clonus could be elicited at either knee or ankle. No sensory change over any part of the lower extremities could be elicited. The left leg was completely paralysed except for slight movement at the ankle and toes. The right leg could be flexed at the hip and

knee, but not extended. The ankle could be both flexed and extended, but plantar flexion was much stronger than dorsi-flexion. The toes could be readily flexed, but extension was weak. There was no localized atrophy of the leg muscles, although all muscle groups were small. The right leg was flaccid and the left moderately spastic.

No change in any modality of sensation could be detected. There was a moderate rigidity of the neck and marked stiffness of the spinal column so that it could not be bent forward. Over the fourth lumbar spine a red hairy naevus about 1.5 cm. in diameter was present, in the centre of which was a minute crust. This entire area was rather firmly attached to the underlying tissues, and was tender to palpation. There was no tumefaction and no palpable spina bifida.

The child was able to sit up alone but unable to maintain that posture unless her hands were kept on the bed behind her to prevent falling backward. She was unable to stand or walk. She had urinary retention necessitating catheterization three or four times daily and enemas were necessary for the evacuation of her bowels.

Roentgenograms taken of the pelvis and lower part of the vertebral column showed incomplete fusion of the laminae of the sacral segments. Blood examinations were negative except for a leucocytosis of 13,600 and 24,200. Urine analysis showed many leucocytes in the sediment but was otherwise normal. During her pre-operative period she had no fever. A lumbar puncture was made between the 5th lumbar and the first sacral spine and thick caseous pus encountered. A syringe attached to the needle aspirated 2 or 3 c.c. of a dirty fluid containing many particles of debris. A culture of this fluid grew *B. coli*.

On March 17, 1934, under general ether anaesthesia, a midline incision was made from the 11th thoracic to the 1st sacral spine, the reddened naevus being excised. Extending from the centre of this area a small white fibrous tube was seen passing between the spines of the 4th and 5th lumbar vertebrae down to the dura to which it was firmly attached. The lamina of the 2nd, 3rd, 4th and 5th lumbar vertebrae were removed. The bone appeared normal. The dura, however, was tense and bluish, and there was a mass at the point where the fibrous tube entered the meninges. The dura, firmly adherent to the arachnoid, was incised at this point and the incision carried through 1.5 mm. of reddish granulation tissue. A cystic cavity 4 to 5 mm. in diameter filled with thick creamy pus and some sebaceous material was encountered. The incision was then extended downward about the mass which lay between the 4th and 5th lumbar vertebrae. Below that, the dura was readily separable from the arachnoid, beneath which the roots of the cauda equina could be seen imbedded in a greyish gelatinous material. The abscess wall, however, did not extend below the level of the 5th lumbar vertebra and the arachnoid was not opened below that point (fig. 3). The skin and fibrous tube were cut off the posterior surface of the arachnoid and pieces were taken from the wall of the abscess for further microscopic study.

In order to reach the upper end of the abscess, the 1st lumbar and 12th thoracic vertebral laminae were removed. After incising the dura beneath the 12th thoracic laminae the posterior surface of the spinal cord was seen. The abscess was then opened up to a point where the cavity seemed to continue downward in a hole which appeared to sink into the dorsal surface of the spinal cord. It was not followed further for fear of injuring the substance of the spinal cord.

The dura was left open and two small soft rubber drains were placed in the abscess cavity and led out from each end of the wound. The muscles and fascia were closed with interrupted catgut and the skin with silk.

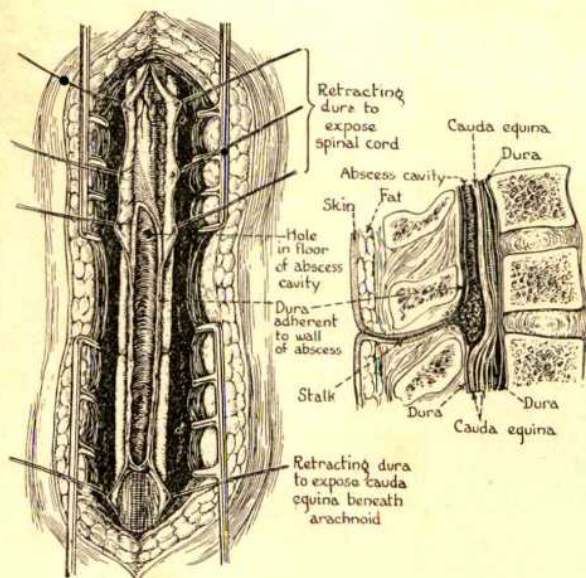


FIG. 3 (Case 2).—Semi-diagrammatic illustration of the operative findings in Case 2. The situation and relation of the meninges and cauda equina to the abscess are shown.

The patient had a slow but uneventful convalescence. Both drains were removed four days after operation, and very little drainage occurred following this. Two weeks after operation the wound was completely healed. Movement in both legs increased, although the right continued to be stronger. Four weeks after operation the patient was able to sit up unassisted, but could not stand even with help. No sensory disturbance could be detected for pain, touch, position or vibration sense. In the right leg the patient had fairly good movement of all muscle groups, but flexion of the left knee was weak, and flexion, inversion and eversion of the left ankle were extremely weak, there being just slight motion against gravity. The right leg was flaccid, the left spastic and painful on movement. Both knee-jerks and the right ankle-jerk were absent, but the left ankle-jerk was greatly exaggerated with a sustained clonus.

PLATE XIV.



FIG. 5.

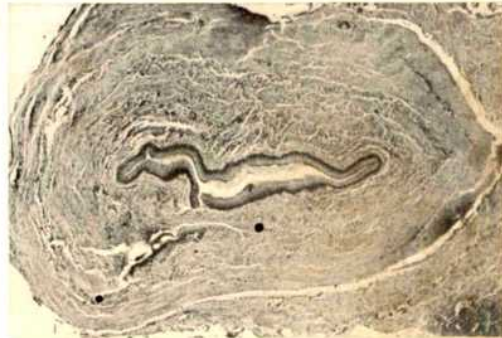


FIG. 7.



FIG. 6.

FIG. 5 (*Case 2*).—Photomicrograph showing the lower end of the dermal sinus penetrating the dura and opening into an inflammatory mass. Hæmatoxylin and eosin.

FIG. 6 (*Case 2*).—A higher power photomicrograph of the small square marked in fig. 5. The nature of the inflammatory reaction is well shown, and its extension into the dura mater is shown by the clumps of cells, mainly small round cells, in the dura mater in the upper half of the illustration. Hæmatoxylin and eosin.

FIG. 7 (*Case 3*).—Cross section of the dermal sinus which led from the skin to the meninges in Case 3. Hæmatoxylin and eosin.

When last seen on May 29, 1934, she was able to walk without assistance, although there was some external rotation and eversion of the foot. All movements of the foot and leg are now possible. She felt quite well and was very lively.

Pathological examination (Plate XIII, fig. 4).—The skin containing the dimple visible on the surface and the subdural mass leading down from it were sectioned serially and stained with hæmatoxylin and eosin, van Gieson's acid picro-fuchsin and impregnated by Perdrau's method.

Sections of the skin revealed a normal surface epithelium, the basilar layer of which contains a brownish pigment. There were the usual papillæ and in the dermis are found many hair follicles, sebaceous and sudorific glands, all apparently perfectly normal. In about the centre of the section is seen an invagination of the epidermis forming a narrow epithelial tube which passes downward into the deeper layers of the skin. The epithelial lining of this tube is very similar to the surface epithelium except that the pigmentation of the basal layer and the normal papillæ are absent. There are a few fine hairs which project from the neighbouring dermal connective tissue through this epithelium into the tube. There are also a few sudorific and sebaceous glands connected with this tube. The lumen is filled with cornified, desquamated epithelial debris. In the connective tissue of the dermis immediately about the tube is a rather marked cellular infiltration. The cells are largely of the lymphocytic series.

Sections of the subdural mass show the downward extension of this epithelial tube. It is similar to that near the orifice on the skin surface except that there are no hair follicles and no glands. Here again there are no papillæ. The tube passes beneath the dura mater, which is continuous with the dense connective tissue sheath of the epithelial tube. The tube terminates a short distance beneath the dura mater, its lower end being open and its lumen communicating with an extensive subdural abscess (Plate XIV, fig. 5).

The subdural abscess is composed of a mass of inflammatory cells of which about half are polymorphonuclear leucocytes and half lymphocytes. There are in addition a few endothelioid cells and a few multinucleated giant cells. These cells are enmeshed in a loose reticulin network. The abscess is intimately connected with the dura mater, strands of which pass into the inflammatory mass (Plate XIV, fig. 6). The remainder of the dura mater is infiltrated by small round cells which lie about the vessels and between the collagenous fibres. There is no epithelium within the abscess other than the extreme lower end of the epithelial tube mentioned above.

This patient's history was not unlike that of the first case. Both were diagnosed as tuberculous meningitis, and both had slowly progressing signs and symptoms of spinal cord involvement with mild remissions. Neither had significant sensory changes either before or after operation. The dermal sinus in this case, as in the first, consisted of an epithelial tube surrounded by collagenous fibrous tissue. However, unlike the first case, it contained dermal appendages and the sinus could

be traced down through the dura, whereas in the former case the sinus could be followed only to the epidural mass of inflammatory tissue. The abscess cavity was much more extensive than in the first case, and it was impossible to extirpate it completely. It is noteworthy that the sinus passed between intact vertebral arches, instead of through a defect in the laminae as in the first case.

The production of an abscess in the subarachnoid space is unquestionably due to the same factors as in the first case—the presence of a long epithelial tube communicating with the skin which readily allows infecting organisms to reach the meninges.

The patient has been followed but a few months, but the improvement in this short time is promising.

Dr. Dallas B. Phemister informed us that some twelve years previously he had operated upon a similar case. He kindly had this patient attend to the out-patient department and secured for us the microscopical preparations of the material removed at operation as well as the entire record of the case. It is through Dr. Phemister's kindness that we are at liberty to include his case with ours in this Report.

Case 3.—T. S. A coloured girl, aged 3 years, was admitted to the Presbyterian Hospital, Chicago, October 21, 1921, on the service of Dr. D. B. Phemister. The patient was the second child in a family of two, born at full term spontaneously. Her development was quite normal, and the parents had noticed no abnormalities except that in the lower lumbar region the patient had a dimple about which were a few hairs. This had been present since birth. At 14 months of age the child had pneumonia, and about the same time a family physician had pulled some hair from the skin surrounding the dimple. Following this it discharged pus for a short time and then healed. Since then it had swollen from time to time, broken down, discharging pus for a period, and then healed again. The area was constantly tender, and the patient complained of severe pain in the back and occasional occipital headaches.

Examination revealed a fairly well nourished young negro girl presenting typical racial characteristics. She was not acutely ill. Physical examination at that time was quite negative except for the local findings. At the level of the spine of the 5th lumbar vertebra in the midline was a hairy, pigmented area in the centre of which a minute hiatus could be detected. The skin was tender on palpation. No neurological examination was recorded. The child walked with the knees semiflexed.

Laboratory examination: The urine and blood were normal, except that there was a leucocytosis of 17,000. Roentgenograms of the spine showed a lack of fusion of the spinous process of the last lumbar and first sacral vertebrae.

On October 25, 1921, the patient was operated upon under ether anaesthesia by Dr. Phemister. An incision about 6 cm. long was made parallel with the vertebral spines over the last lumbar and sacral vertebrae. The hairy pigmented area surrounding the minute opening in the skin was excised. A probe put into the hiatus was seen to pass down a stout fibrous tube through a defect in the spinous processes of the 5th lumbar vertebra, and to rest upon the spinal meninges. In removing the fistulous tract the meninges were opened and about six drops of glairy, gelatinous, slightly purulent material escaped through the rent. In order completely to remove the sac a part of the dura had to be cut away. Within this, what appeared to be a friable sac wall was dissected free from the nerve roots. The dura was left open and cerebrospinal fluid escaped freely. The fascia was closed with catgut and the skin with silk. One plain gauze was left in the wound and removed the following day. On October 27, 1921, two stitches were removed and a few cubic centimetres of pus expressed. For a week dark-brown pus drained freely from the wound, and then the discharge gradually decreased and the wound granulated, so that on the patient's discharge on November 15, 1921, it had completely healed.

The patient was seen again on March 2, 1934. Her mother stated that following the operation in 1921 the patient's gait had rapidly improved, and that she had no bowel or bladder disturbance. At that time, March 2, 1934, she had no complaint, and her mother regarded her as normal. Examination showed that the operative scar was well healed with no swelling. There was no sensory loss in any part of the body, no motor weakness, and the gait was normal. The knee and ankle jerks on both sides were absent.

Pathological examination.—Through the kindness of the pathological laboratory of the Presbyterian Hospital, a slide containing three pieces of tissue was examined. The first specimen is a cross-section of heavily pigmented epidermis and subcutaneous connective tissue. Numerous dermal appendages, sweat and sebaceous glands and hair follicles are present, and present no abnormality. There is a small irregular depression in the centre of the epidermis containing cornified epithelial debris on one side and the opening of a hair follicle on the other, possibly the stoma of the dermal sinus. The second piece of tissue is a cross-section of a small tube of stratified squamous epithelium showing no pigment in the basal layers. It is surrounded by a thick layer of collagenous connective tissue and outside of this is considerable adipose tissue. The lumen of the tube contains a small amount of cornified epithelial debris. The inner surface of the epidermis is devoid of papillae, and no dermal appendages are seen. Occasional small round cells are scattered throughout the connective tissue surrounding the epithelial tube (Plate XIV, fig. 7). The third section is a fibrous and collagenous connective tissue studded with small abscesses. These are composed of masses of small round cells and phagocytic cells. In other areas small collections of these cells are present without any evidence of central necrosis. A few polymorphonuclear cells are present. At one corner of this specimen a small piece of epidermis

identical with that seen in the first piece of tissue is present, and in the opposite corner an arc of epithelial tissue, probably a small segment of a hair follicle.

Even with these few sections it is evident that the condition present in this case is very similar to that in the first two patients. The extent of the dermal sinus is unknown, but as demonstrated grossly it probably extended at least to the subdural inflammatory mass.

As in the previous cases an epithelial tube leading from the skin to an inflammatory mass beneath the dura mater was found at operation. The histopathology of this was similar to that of the specimens from the first two cases. However, it is interesting to note that there was no pigment in the basal layers of the epithelium of the tube, such as was present in abundance in the normal epidermis. The same phenomenon was noted in Case 2 in which the surface epithelium, though from a white girl, was heavily pigmented, whereas that from the tube contained no pigment.

Dr. Samuel C. Harvey, of the Yale University School of Medicine, has also informed us that several years ago a similar case was operated upon in his clinic. This case was recorded by Moise [5] and is related here in detail.

Case 4.—A white male, aged 18, was admitted to the New Haven Hospital on September 10, 1924. He had always had in the lower lumbar region a sinus discharging a watery fluid at short intervals. A week before admission the skin about the sinus became tender, and two or three days later his back began to ache. The day before admission he had headache, general malaise and anorexia. There was no nausea, vomiting or convulsions. When admitted his temperature was 101.8° F., pulse 86, and respirations 20 per minute. He appeared ill, his face was flushed, and his expression anxious. The heart, lungs and abdomen were normal. Neurological examination showed a very stiff neck, normal tendon reflexes in the upper extremity, but absent knee and ankle jerks. Kernig's sign was present. In the midline over the upper sacral region was an area of red and tender skin surrounding a small sinus from which some thin pus could be expressed.

A roentgenogram of the sacrum showed a sacralization of the 5th lumbar vertebra, an irregularity in the fusion of the spines of the 5th lumbar and the 1st sacral vertebrae, and a flattening of the spine of the 1st sacral segment with a defect below this level.

Lumbar puncture provided a cloudy cerebrospinal fluid under increased pressure containing 1,450 cells per cubic millimetre, predominately polymorphonuclear leucocytes. A few Gram-negative cocci were seen in smears, and culture showed hæmolytic *Staphylococcus albus*. Daily lumbar puncture failed to improve his condition, so operation to remove the sinus was advised.

Operative note: September 23, 1924. The sinus was injected with methylene blue and excised with the surrounding tissue. The sinus extended through a small bony defect, measuring 1 cm. in diameter, just to the right of the midline at the junction of the 1st and 2nd sacral vertebrae. The incision was then extended and a laminectomy performed. The spine of the 1st sacral vertebra was flat and was removed. The underlying dura was stained deeply with methylene blue. There was a tuft of granulation tissue just beneath the defect in the spinal column. This was excised after the dura had been opened. A small rubber tissue drain was inserted through the upper part of the incision down to the dura. The wound was closed in layers.

Histological examination of the excised sinus showed it to be a tube lined with several layers of stratified squamous epithelium surrounded by a dense fibrous wall.

The patient rapidly improved following operation, although for several days he suffered severe pains in his back and legs. Spinal fluid drained from the wound for nine days. At the time of discharge the patient felt quite well, and there were no neurological abnormalities.

The author considered this case an example of pilonidal sinus which, instead of ending blindly, communicated with the subarachnoid space through a defect in the spines of the sacral vertebrae. It is evident that this is similar to the previously mentioned cases, and the only unusual finding is the direct opening of the tube into the subarachnoid space rather than into an inflammatory mass about the meninges. It is likely, however, that this communication was secondary to the infection and was not present in the original congenital defect.

A careful review of the literature has revealed three additional cases. A case almost identical with that described by Moise was reported by Ripley and Thompson [1] in 1928.

Case 5.—D. L., male, aged 3½ months. The patient had a normal birth. For two weeks prior to admission he had been fretful, screaming when lifted. On admission the child had a temperature of 101.4° F., pulse 148, respirations 48. Physical examination revealed consolidation of the right upper lobe of the lung. Four days later, although the child's condition was slightly improved, pus was noted at the bottom of a sacro-coccygeal dimple, and a probe was slipped in 4 cm. without encountering resistance. On lumbar puncture 2 cm. of thick yellowish pus was removed by aspiration. Examination of a smear of the material showed *Staphylococcus albus*. Operation was then performed, excising the sinus as high as the lumbo-sacral junction. One part of the sinus lay within the sacral canal. The second sacral arch was absent. A drain was inserted and the wound closed.

When opened the sac removed at operation was found to contain sebaceous material and a hair. Microscopical study of the sinus showed it to be of the same structure as normal skin with an inflammatory reaction about it.

The wound drained poorly and the patient's general condition became grave. Lumbar puncture was performed once or twice daily to drain the spinal fluid and relieve the intracranial tension. On the eighth day after operation the spinal fluid appeared clear but was under considerable pressure and contained 430 cells mainly polymorphonuclear leucocytes. The patient died on the ninth post-operative day. At autopsy methylene blue injected into the lumbar subarachnoid space was found in the operative wound. There was a very marked purulent exudate over the surface of the cerebral hemispheres.

This case is identical with that reported by Moise. Whether death was due to the defective drainage of the sinus, or to the failure of spinal fluid to escape from the wound, cannot be said.

The second case found in the literature is apparently similar to the first three of the above five cases, although there is no note as to the depth of the dermal sinus, and hair was found at its base. It was reported by W. and N. Sharpe [8] (pp. 269-371) as a case of intradural dermoid.

Case 6.—F. S., male, aged 3 years, was apparently a normal child except for a small pinhead-size depression over the spine in the lumbar region present since birth. His back was rigid, and from time to time a thick yellow discharge appeared at the site of the depression. Several operations superficially excising the sinus only left the patient with a marked weakness of both legs. The wound broke down and continued to drain purulent material.

At 3 years of age there was a spastic paralysis of both lower extremities but no sensory changes in any part of the body. Roentgenograms showed a defect in the left lamina of the 11th thoracic vertebra. A laminectomy was performed with excision of the fibrous sinus which was attached to an inflammatory mass about the posterior aspect of the dura. When this was opened around the nodule a mass of caseous material containing hair was found imbedded between the dura and the left side of the spinal cord. This was removed, a drain inserted and the wound closed.

The wound healed slowly, but otherwise the convalescence was uneventful. Motion returned in the legs in three weeks, and within a year he was able to walk well, although the left leg was dragged slightly.

No pathological description of the tissue removed is given, but it seems probable that this is another example of a dermal sinus extending downward through unfused lamina to end around the spinal cord. The striking point was the presence of hair at the base of the sinus, a phenomenon which is not unexpected since in the second case there was hair in the upper portion of the sinus.

All of the above six cases of congenital dermal sinuses were asso-

ciated with evidence of meningeal irritation and infection due to infected material having passed down the sinuses to these tissues. Clark [1] has reported a case which seems similar to these, although there was at no time any evidence of meningeal infection, nor was the nature of the lesion confirmed at either operation or necropsy.

Case 7.—L. N., female, aged 13 years. Her development was normal. It was noted that from birth the patient had a small depression in the median line between the 4th and 5th cervical spines out of which grew a small tuft of hair about half an inch in length. She lacked dexterity and speed in executing delicate movements with her fingers and hands, but there was no atrophy or motor weakness except a slight deficiency in adduction, abduction, flexion and extension of the little and ring fingers of both hands. • The remainder of the neurological examination was quite negative.

Roentgenograms showed no defect in the 4th or 5th cervical vertebra but a cleft in the arch of the 3rd.

- From the clinical description it is, of course, impossible to be certain of the exact nature of the lesion, but it is not unlikely that this is an example of the same malformation which has not yet become infected.

A careful search of the literature has failed to reveal further examples of this congenital malformation. The similarity of all seven cases, and the evident mode of infection through the dermal sinus, is quite striking and merits recognition as a clinico-pathological entity. The fact that two of these cases presented a clinical resemblance to tuberculous meningitis is still greater reason for the consideration of this congenital anomaly in any chronic meningitis, particularly as operation offers such an excellent result. The presence of the minute opening of the sinus in the skin, commonly referred to as a dimple, from which a discharge occurred at intervals, had been noted by the parents in all cases associated with meningeal irritation, before the patients were referred to a physician. This anomaly when accompanied by the typical history of fever, stiffness and tenderness of the back, neck rigidity, some degree of motor weakness in the lower extremities and the finding of a pleocytosis in the spinal fluid, should suffice to make possible the diagnosis of infected congenital dermal sinus extending to the spinal meninges.

Association with spina bifida.—It will be noted that every case was associated with a defect in the posterior neural arch which could be demonstrated radiographically. However, the defect demonstrable in the second case is the normal state for the sacral vertebræ at this age and cannot be considered as having any association with the congenital

dermal sinus which, unlike the condition found in the other cases, passed through the opening normally present between the laminae of the 4th and 5th lumbar vertebrae. Thus, although it can be stated that this peculiar malformation is usually associated with a spina; bifida it is not necessarily so.

Although spina bifida occulta is generally considered as of not infrequent occurrence, there are very few statistics on which to base this conclusion. Mayer [4] states that a complete splitting of the sacrum occurred in 3 per cent. of cases, and that in children over 10 years of age the first sacral lamina was not fused in 24 per cent. of cases in the general population. These figures indicate a much higher incidence of spina bifida than that reported by Sutherland [9] at the Mayo Clinic. In approximately 12,000 roentgenograms of the spine he found 621 cases of spina bifida, an incidence of slightly more than 5 per cent. The condition was twice as common in males as in females. It involved the 1st and 2nd sacral vertebrae in 70 per cent. of cases, the 5th lumbar in 24.5 per cent. No mention is made of the incidence of spina bifida occulta in the thoracic region, but four cases are presented with the defect in that region.

In 1920 Theodora Wheeler reviewed the literature to that time, and in a group of 1,000 consecutive X-ray plates of the sacrum found the incidence of spina bifida occulta of the first sacral vertebra to be 13.1 per cent., and the laminae of the entire sacrum were unfused in 2.89 per cent. of cases. The 5th lumbar was found unfused in 23 cases of the 1,000, and the atlas, the only other vertebra in that series with spina bifida, in 1.47 per cent.

Table I shows the incidence of spina bifida occulta in a series of roentgenograms of the spine taken at the University of Chicago Clinics in the past six years. These include films taken to show trachea, cervical spine, colon, chest, thoracic spine, lumbar spine, urinary tract, pelvis, sacro-iliac joints, and lumbo-sacral spine; some of which only incidentally showed the vertebrae. The total number of patients of whom roentgenograms of these parts were taken was noted, and then twenty representative roentgenograms of each studied to determine the mean number of vertebrae included in any roentgenogram of any of the above structures. From these data it was a simple mathematical problem to calculate the number of times each vertebra had been shown in the total number of roentgenograms. All cases of spina bifida occulta were then collected and reviewed to determine the location of the anomaly, its association with enuresis, motor or sensory defects, local

manifestations such as hirsuties or lipoma, and other congenital abnormalities. These data are given in tabulated form in Table II. In all 123 cases of spina bifida occulta, of which seventy-five were in

TABLE I.

Vertebra	No.	Total number Roentgenograms	No. of spina bifida	Percent- age
Cervical ..	1	598	1	0.17
	2	785	0	0.00
	3	913	0	0.00
	4	1,149	0	0.00
	5	2,815	1	0.03
	6	4,088	1	0.02
	7	5,881	2	0.04
Thoracic ..	1	5,406	4	0.09
	2	4,989	5	0.10
	3	4,284	2	0.05
	4	2,182	4	0.18
	5	1,456	1	0.07
	6	1,500	1	0.07
	7	1,427	1	0.07
	8	1,770	1	0.06
	9	2,685	1	0.04
	10	3,584	1	0.03
	11	4,421	0	0.00
	12	5,967	1	0.016
Lumbar ..	1	6,290	1	0.016
	2	6,712	2	0.03
	3	6,594	2	0.03
	4	7,680	4	0.05
	5	7,516	28	0.37
Sacral ..	1	6,945	118	1.62
	2	6,301	41	0.65
	3	6,301	32	0.51

TABLE II.

	No. of cases	Enuresis	Sensory disturb- ance	Motor disturb- ance	Local manifes- tations (hair, dimple, &c.)	Other congeni- tal abnor- malities	No signs nor symptoms directly referable to lesion	Low back pain
Cervical	2	0	0	0	0	1	1	0
Thoracic	9	1	0	1	1	4	2	0
Lumbar	1	0	1	1	1	1	0	0
Lumbo-sacral (L ₁ -S ₅)	111	16	8	5	11	16	78	42

males and forty-eight in females, were found. The most frequent site of the defect was in the lumbo-sacral region, 111 occurring there. Nine were present in the thoracic region, but in none except the first case

reported here was there any external manifestation of the defect, but four had scoliosis and other skeletal abnormalities. Three had several hemivertebrae and two of these had associated anomalies of the ribs.

Genesis of congenital dermal sinuses.—The consideration of the development of these congenital dermal sinuses leads to a discussion of the theories advanced for the aetiology of pilonidal sinus. In 1892 Mallory [3] came to the conclusion that these malformations were due to a failure of obliteration of the medullary canal in the coccygeal region. This view has found much support, the most recent coming from Weeder [11] in an article in 1933. It is obvious, however, that this theory will not explain the presence of these dermal sinuses in any

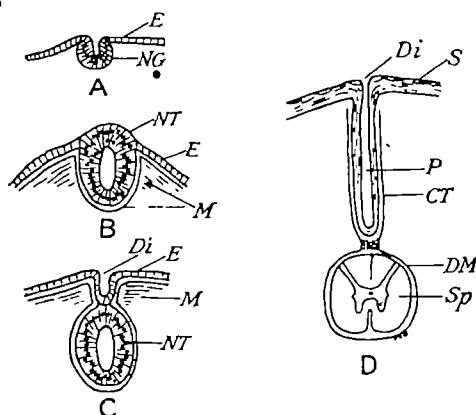


FIG. 8.—Sketch illustrating the possible development of the malformation: E., ectoderm; N.G., neural groove; N.T., neural tube; M., mesoderm; Di., dimple; S., skin; P., congenital dermal sinus, C.T., connective tissue sheath of sinus; D.M., dura mater; Sp., spinal cord.

region of the body but the sacro-coccygeal, and that some other explanation must be given for their presence in the lumbar, dorsal and cervical regions.

The conclusion would seem justifiable that at the time in embryological development (the first month of intra-uterine life) when the cutaneous epithelial ectoderm and the neuro-epithelial ectoderm should have separated, the cleavage between them was incomplete at the particular point where the sinus occurred. Thus, the neural tube carried down with it a narrow invagination of the skin, clothing it with a mesodermal covering continuous with its own connective tissue covering, the meninges. The cause of this abnormal development remains one of the unexplained perversities of intra-uterine development. We have attempted to illustrate this interpretation of the development of this

condition in the accompanying sketch (fig. 8). Whether this same explanation of the ætiology is true for pilonidal sinuses cannot be stated, but it is at least a possibility (Stone [10]).

SUMMARY.

1) Seven cases presenting a clinico-pathological entity are described. A congenital dermal sinus manifested externally by a small dimple in the midline of the back becoming infected, discharges periodically serous or purulent material. This sinus extends to the meninges and its lumen acts as a pathway for infection to reach these structures. When this occurs, producing abscess formation, fever develops, the back becomes painful and rigid, and the neck stiff. Weakness of the lower extremities ensues, but sensory disturbances are slight or absent. The spinal fluid, usually sterile, shows a pleocytosis.

(2) Surgical removal of the sinus and subdural abscess with drainage produces a complete cure in almost every case.

(3) The relation of this congenital dermal sinus to spine bifida occulta is discussed and the incidence of the latter in a series of 7,500 roentgenograms taken of the spine in a general medical and surgical clinic is given.

(4) The ætiology of these congenital dermal sinuses and pilonidal cysts is discussed.

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SOME ASPECTS OF SWEAT SECRETION IN MAN: WITH SPECIAL REFERENCE TO THE ACTION OF PILO- CARPINE.

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It has long been known that the general antagonistic relationship between the sympathetic and parasympathetic divisions of the autonomic nervous system breaks down in the case of the sweat glands of man and of the cat. The sweat glands, though supplied solely by nerves which are anatomically sympathetic, react to drugs as if supplied by parasympathetic nerves. Recently, however, physiological investigation has provided, in the theory of chemical transmission of autonomic nerve impulses, a more or less satisfactory explanation of this puzzling anomaly as regards, at least, the reactions of the glands of the cat.

Since the initial experiments of Loewi (1921) the evidence for chemical transmission of the impulses of autonomic nerves has grown steadily and of late years with great rapidity. In a general survey of the evidence Dale (1934) has pointed out that for all autonomic pre-ganglionic fibres the transmitter is acetyl choline. For all parasympathetic post-ganglionic fibres the transmitter is also acetyl choline, while for most sympathetic post-ganglionic fibres it is an adrenaline-like substance or possibly adrenaline itself. For some sympathetic post-ganglionic fibres, however, the transmitter is again acetyl choline. To adopt Dale's classification (1933), which is based on function and not on anatomical distribution, autonomic nerve-fibres may be cholinergic or adrenergic. Dale and Feldberg (1934) have now established that the post-ganglionic fibres to the sweat glands of the cat's paw are sympathetic cholinergic fibres, and they consider as justifiable the assumption that the human sweat glands are similarly innervated. More direct evidence on this point is, however, desirable since there is some evidence that the human sweat glands may react to pilocarpine differently from those of the cat.

The responses to pilocarpine of the sweat glands of the cat's paw

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were studied by Langley and Anderson (1904); Langley (1922) and, in considerable detail, by Burn (1922, 1925). They established (1) that the sweating produced by pilocarpine occurred after division and degeneration of the secretory nerves, and (2) that the response to pilocarpine might occur, though usually in greatly diminished amount, after division and degeneration of all nerves to the part. Their conclusions were that pilocarpine acted peripherally and on the sweat glands directly. Other views have been expressed regarding the action of pilocarpine in man. Horsley (1910) used pilocarpine as a test for the level of spinal cord lesions, a test which implied, in reality, a belief that the drug acted on the central nervous system. As late as 1929 the view was held (3) that pilocarpine acted on the sympathetic nerve-endings. This view was shown to be untenable by Lewis and Landis (1927) and subsequently by others as the practice of surgical removal of sympathetic nerves became common. A more popular assumption (Billigheimer (1921), Woolard and Norrish (1933)) was that pilocarpine acted on some fibres in the spinal nerves other than the secretory sympathetic fibres. On that assumption is based a theory that the human sweat glands have a double innervation.

Recently Cushing (1931) has brought forward suggestions of great interest and importance regarding the action of pilocarpine in man. From observations on the effects of injecting pituitrin and pilocarpine into the cerebral ventricles he concluded in favour of a "parasympathetic centre" in the hypothalamus which could be stimulated by such substances injected intraventricularly, and he believed that the normal excitant to the centre was the hormone of the posterior lobe of the pituitary. The experimental evidence in support of such a centre is certainly strong; a full account is given in Cushing's papers. There seems also little doubt that the responses which he observed to intraventricular injection of pituitrin or pilocarpine were actually of central origin. He suggested further, however, that pilocarpine, when introduced subcutaneously or intramuscularly in man, might act partly or wholly on a hypothalamic centre and not, as had previously been generally supposed, peripherally. With the last suggestion the present investigation is mainly concerned.

I.—THE POSSIBLE CENTRAL ACTION OF PILOCARPINE.

The possibility that pilocarpine when introduced subcutaneously caused sweating by acting on a hypothalamic centre was tested by observations of:—

(1) The sweating response to the drug in areas to which the various types of nerves had been divided.

(2) The effects of intraventricular injection of pilocarpine in cases of hydrocephalus.

(3) The effect of injection into the skin.

A.—The Sweating Response after Nerve Division and Degeneration.

Methods.—The area chosen for study was the face, where sweating could be readily observed. The motor, sensory or sympathetic nerves to the face had been separately severed at operation, or paralysed by injection of alcohol, in the subjects of investigation. The conditions for which operation was carried out need not be discussed. When pilocarpine was injected care was taken to exclude the effects of heat or of emotion. Injections of normal saline solution were used as controls. Sweating was observed with the aid of a magnifying lens ($\times 8$), in a good light. Skin temperatures were recorded in all cases by means of a thermocouple arrangement.

Loss of motor and sensory function was tested in the usual way. Loss of sympathetic supply was tested by warming the body under a heating cage while protecting the face from direct exposure to heat. The desympathectomized area remained pale and dry in contrast to the flushed and sweating skin with normal sympathetic innervation. It was found that skin in an area of sympathetic paralysis sometimes acquired during the test a greasy moist appearance, probably from secretion of sebaceous glands. The warming was therefore continued until profuse sweating appeared in normally innervated areas.

The period allowed for degeneration of nerves after operative division was at least three weeks.

(1) *Motor nerve degeneration.*

Case 1.—A boy, aged 11, had sustained an injury at birth to the left facial nerve followed by complete and permanent facial paralysis. The flushing and sweating response to warming the body was simultaneous and practically identical on both sides. The same result followed subcutaneous injection of 10 mgm. pilocarpine.

Inference.—Motor nerve degeneration had no effect on the sweating response to pilocarpine.

The response to heat showed that the secretory fibres to the sweat glands were intact. They are not, therefore, distributed with the facial nerve.

(2) *Sensory nerve division without degeneration.*

Case 2.—A woman, aged 57. Complete section of the sensory root of the left trigeminal nerve had been carried out eight months before. There was no degeneration of the distal axons as the nerve had been sectioned proximal to the Gasserian ganglion.

The sweating responses to warming the body and to subcutaneous injection of 12 mgm. of pilocarpine were simultaneous and equal on both sides of the face.

Inference.—Sensory nerve division had no effect on the response to pilocarpine. The response to warming the body showed that the secretory fibres to the sweat glands of the face were everywhere intact. Therefore, if the secretory fibres are distributed with the branches of the trigeminal nerve, they must join the nerve at or distal to the Gasserian ganglion.

(3) *Sympathetic nerve degeneration and sensory nerve division on one side of face.*

Case 3.—Man, aged 40. A complete section of the sensory root of the right trigeminal nerve had been carried out two years previously, and the superior cervical sympathetic ganglion on the same side had been excised four months previously. Thus on the right side of the face the sympathetic nerves had degenerated (assuming that the post-ganglionic fibres to the sweat glands of the face have their cell-stations in the superior cervical ganglion), and on the same side there was sensory nerve division without degeneration.

Warming the body revealed a condition of sympathetic paralysis of the right side of the face.

Subcutaneous injection of 15 mgm. of pilocarpine evoked a sweating response on both sides of the face. The response was excessive and prolonged in the desympathectomized area.

Inference.—The sweating response to pilocarpine remained after degeneration of the sympathetic secretory nerves and in this case the response was excessive.

(4) *Sympathetic nerve degeneration on one side and sensory nerve degeneration on the opposite side.*

Case 4.—Man, aged 39. The left superior cervical sympathetic ganglion was excised and a portion of the right supraorbital nerve resected. The right supraorbital artery was injured and required ligation. The conditions were sympathetic paralysis of the left side of face and sensory nerve paralysis of part of the right forehead.

The reaction to warming the body was observed at forty-eight hours and again on the twenty-third day, when the nerves had degenerated. On both occasions no sweating appeared on the left side of the face and profuse sweating

was elicited in normally innervated areas. On the right forehead the distribution of sweating in the anæsthetic area was different at each test. At forty-eight hours the area which was completely anæsthetic to pin-prick and light touch remained dry, although some sweating occurred at the lateral edge in areas of partial anæsthesia (fig. *a*). On the twenty-third day the area which remained entirely dry was much reduced in size. Its medial edge was not altered, but sweating appeared over part of the anæsthetic area on its lateral side (fig. *b*).

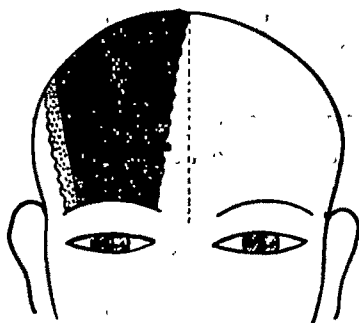


FIG. a. CASE 4.

Response to warming the body in the area of sensory paralysis at 48 hours.
 [Stippled] sweating. [Solid black] no sweating.



FIG. b. CASE 4.

Response to warming the body in the area of sensory paralysis on the 23rd day.
 [Stippled] sweating. [Solid black] no sweating.

On the twenty-third day subcutaneous injection of 15 mgm. of pilocarpine evoked an excessive sweating response over the entire right forehead, a well-marked response in normally innervated areas, and a moderate response over the left side of the face.

Inference.—The sweating response to pilocarpine occurred after degeneration of sensory nerves, and in this case the response was excessive. The response after degeneration of sympathetic nerves was very slightly below normal.

The test of warming the body at forty-eight hours suggested that the secretory fibres to the sweat glands had been severed in the supra-orbital nerve. The second test on the twenty-third day gave a surprising result, which showed that many of the secretory fibres in the lateral part of the anæsthetic area were intact. The result will be discussed later.

(5) *Sympathetic nerve division and sensory nerve degeneration on the same side of the face.*

Case 5.—Man, aged 50. The left sympathetic trunk was injected with alcohol from the level of the inferior cervical ganglion to that of the 4th thoracic

ganglion, and, in addition, the left supraorbital and supratrochlear nerves were divided.

There was thus a sympathetic paralysis on the left side of head, neck and upper extremity. Degeneration of post-ganglionic fibres to the face did not follow from the alcohol injection. Over an area on the left forehead the sensory nerves were divided and subsequently degenerated (fig. c).

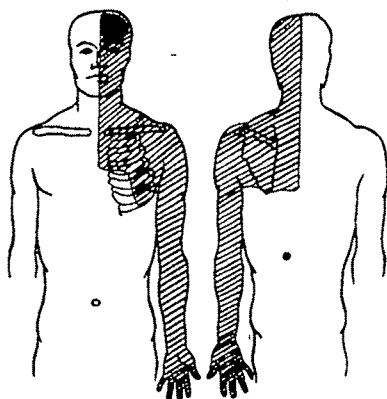


FIG C. CASE 5

▨ Area of Sympathetic Paralysis
 ■ Area of Sympathetic and Sensory Paralysis

Warming the body was carried out on the fourth and thirty-second days, and no sweating appeared on the left side of the face.

Subcutaneous injection of 15 mgm. of pilocarpine on the third day produced approximately equal sweating on both sides of the face. On the thirty-first day the sweating response to the injection was considerably reduced over the whole desympathectomized area as compared with normally innervated parts. In the forehead area the response was very slight though definite.

Inference.—In this case the response to pilocarpine was reduced after an interval of thirty-one days following sympathetic nerve division. The response was greatly diminished where sensory nerves had degenerated.

Case 6.—Man, aged 20. The left sympathetic trunk between the superior cervical and middle cervical ganglia was resected and the left supraorbital and supratrochlear nerves were divided. The conditions were similar to those in Case 5 (fig. c).

Sympathetic paralysis was confirmed by warming the body on the eighth and thirty-fourth days.

On the seventh day the response to pilocarpine in the left forehead area

was greatly diminished, while in the remainder of the desympathectomized area sweating was excessive.

On the thirty-second day the response in the forehead area was absent or uncertain, and in the remainder of the desympathectomized area it was delayed though ultimately as profuse as on the right side.

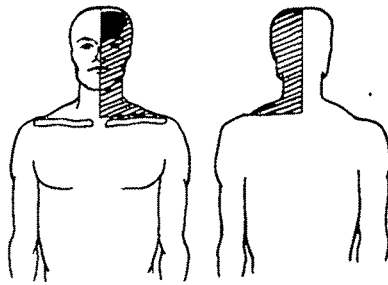


FIG. d. CASE 6

▨ Area of Sympathetic Paralysis

■ Area of Sympathetic and Sensory Paralysis

Inference.—Sensory nerve degeneration led in this case to abolition of the sweating response to pilocarpine. Sympathetic nerve division was followed by an excessive response on the seventh day but by a delayed response on the thirty-second day.

Discussion: The site of action of pilocarpine.—It is evident from these observations that division of all types of nerves to the face did not prevent the sweating response to pilocarpine injected subcutaneously. Therefore the drug did not act wholly or mainly on a centre in the brain. Sweating to pilocarpine occurred also after degeneration of all types of nerves, and thus the response was obviously not dependent on the presence of undegenerated nerve-fibres. Pilocarpine then must act not only peripherally but on the sweat glands directly.

The changes in the sweating response after nerve division and degeneration.—We have seen that after sympathetic nerve division the response to pilocarpine could be normal, excessive, delayed or reduced; after degeneration of the same nerves it could be excessive or normal. After sensory nerve division it could be excessive, reduced or absent: probably the usual result is a considerable reduction. Motor nerve degeneration did not effect the response. It is clear that changes in response are variable, and cannot be predicted with any certainty. There are, however, two main tendencies. One is for sympathetic nerve degeneration to be associated with an excessive response, and the

other for sensory nerve degeneration to be associated with the diminished response.

Diminution or absence of response is an old experimental observation. Burn, who found that denervation of the cat's limb led to diminution or failure of the response to pilocarpine in the sweat glands of the pad, at first (1922) attributed the change to the loss of vascular responses occasioned by sensory nerve degeneration. Later (1925) he considered that disuse of the limb from motor paralysis was the chief factor. In the present investigation on man degeneration of the motor nerves to the face muscles caused no great alteration in the sweating response to pilocarpine, probably because disuse of the facial muscles had little effect on the vascular conditions in the skin of the face. Sensory nerve degeneration would seem, from the present investigation, to be the most potent cause of diminution of the pilocarpine sweating response, probably because it is accompanied by alterations in the local vascular responses. When sympathetic nerve division is associated with delay or reduction of the response, the explanation may be sought in the disuse of the sweat glands.

Failure of the sweat glands of a paralysed limb to react to pilocarpine has frequently been observed in man, and the observation is not surprising. The sweat glands of the limb are less active than those of the face, and, when the nerves have degenerated, disuse of muscles and of sweat glands and loss of vascular responses are combined to militate against the response to the drug. The observation, however, is not evidence that pilocarpine acts otherwise than on the sweat glands directly.

The exaggerated response to pilocarpine after sympathectomy was observed in two subjects. No constant relationship was found between sweating after pilocarpine and increased blood flow as estimated by a rise of skin temperature. On one occasion the temperature of a normally innervated area immediately before the onset of profuse sweating after pilocarpine was 2° C. lower than that of a corresponding desympathectomized area in which little or no sweating occurred. Again, it was found that the temperature of a desympathectomized area with excessive response to pilocarpine was no higher than that on the normal side. The exaggerated response was thus not solely a result of increased blood flow. The denervated glands apparently become hypersensitive to the drug. Anderson (1905) found the same change in the denervated pupil. The change is no doubt related to the exaggerated response to adrenaline after sympathetic degeneration (Elliott, 1904).

The distribution of the secretory fibres to the sweat glands of the face.—Sweating produced by warming the body indicates the presence of sympathetic secretory fibres. The response is due to central stimulation and the impulses are transmitted solely by the known secretory fibres. In the face these fibres may be distributed with motor or sensory nerves or with the vessels.

The responses to the test in Case 1 and Case 2 showed that the secretory fibres are not distributed with the facial nerve and that they are not severed in the sensory root of the trigeminal nerve. If they are distributed with the peripheral branches of the trigeminal nerve they must join the nerve at or distal to the Gasserian ganglion. The first test in Case 4 appeared to indicate that division of the supraorbital nerve severed the secretory fibres over an area corresponding roughly with that of sensory paralysis, and to support the view that the fibres are distributed with the peripheral branches of the trigeminal. On the twenty-third day, however, the area of secretory paralysis was considerably smaller than that of sensory paralysis. The conditions were complicated by injury to the artery, and it is possible that the secretory fibres are distributed with the vessels. The question can only be decided by further observations.

B.—The Effects of Intraventricular Injection of Pilocarpine.

The reaction to intraventricular injection in normal human subjects of a small quantity (2·5 mgm.) of pilocarpine was described by Cushing. The effects were nausea, vomiting, retching, flushing and sweating, a rise in systolic blood-pressure and a fall in body temperature. There were no pupillary changes. The sweating response was much more marked and prolonged than that after subcutaneous injection of a larger quantity of the drug (12·5 mgm.). The effects, he considered, were a result of stimulation of a hypothalamic parasympathetic centre by the drug after resorption through the ependyma. The reaction failed in cases of severe hydrocephalus, and the failure he attributed not to changes in ependyma or choroid plexus, nor to dilution of the drug in excess of fluid, but to destruction or functional impairment of the centre by prolonged stretching of the anterior wall of the third ventricle. In support of his contention he quoted a failure of response in a case where a tumour had destroyed the anterior wall of the third ventricle but had not caused hydrocephalus. We have used the failure of response in hydrocephalus to test the possible central action of pilocarpine when introduced subcutaneously or intravenously.

Methods.—The subjects of study were infants with hydrocephalus. The block of the cerebrospinal fluid circulation was proved in all to be extraventricular, either by observation at operation or by injecting dye into the ventricle and recovering it from the lumbar fluid. The interval which elapsed between injection of the dye and its appearance in the urine provided an indication of the severity of the block and of the time at which peripheral effects might appear. Warming the body was employed as a test of the integrity of secretory fibres to the area studied, and of the presence of sweating centres in the central nervous system.

TABLE I.
Case 7. — Male, age 2 months.

Procedure.	Sweating.	Flushing.	Vomiting.	Heart Rate.	Rectal Temp.	Other Effects.
Injection of 2.0 mgm. pilocarpine subcutaneously.	Appeared at 12 mins. Moderate.	Appeared at 12 mins; lasted 25 mins; followed by pallor.	At 15 and 17 mins.	Rise began at 13 mins. Maximum rise of 36 beats at 17 mins.	No change.	Salivation. Reaction followed by slow pulse at 40 mins.
Injection of 1.625 mgm. pilocarpine intravenously. Reaction stopped by atropine at 11 mins.	Appeared at 1 min. Slight.	Immediate; lasted 2 mins; followed by pallor.	Nil. Retching at 3 mins.	Slowing at 3 mins. Maximum fall of 60 beats at 8 mins.	No change.	Salivation. Main features: slow pulse, fall in blood pressure.
Injection of 2.5 mgm. pilocarpine intraventricularly.	Nil.	Nil.	Nil.	Uncertain. Probably slight slowing of 20 beats.	No change.	No effect of any kind.
Warming the body.	Flushing and sweating in all areas.					

The responses to pilocarpine introduced subcutaneously, intravenously and intraventricularly were compared and control injections of normal saline were made.

Two cases suffice for illustration.

Case 7.—Male infant, aged 2 months. The pathological conditions were a dorsal spina bifida of the myelomeningocele type and severe hydrocephalus. The results of investigation are shown in Table I.

Case 8.—Male infant, aged 5 months. The pathological conditions were a sacral spinabifida of the myelomeningocele type and hydrocephalus of moderate degree, which had apparently remained stationary for about one month. The results of investigation are shown in Table II.

TABLE II.

Case 8. - Male, age 5 months.

Procedure.	Sweating.	Flushing.	Vomiting.	Heart Rate.	Rectal Temp.	Other Effects
Injection of 2.5 mgm. pilocarpine subcutaneously.	Appeared at 8 mins. Moderate.	With sweating.	Once at 14 mins.	Slowing began at 8 mins. Maximum fall of 40 beats at 22 mins.	Fall of 0.9° F. in 42 mins.	Salivation.
Injection of 1.0 mgm. pilocarpine intravenously	Appeared at 1 min. Lasted 9 mins. Moderate.	Immediate. Lasted 1 min. followed by pallor.	Nil.	No definite change, or very transient slowing.	No change.	Salivation; lachrymation slight.
Injection of 2.5 mgm. pilocarpine intraventricularly.	Appeared at 14 mins. Moderate.	Slight, with sweating.	Frequent after 8 mins.	Slowing began at 19 mins. Maximum fall of 40 beats at 28 mins.	Fall of 1.6° F. in 30 mins.	Salivation.
Injection of 2.5 mgm. pilocarpine into lumbar C.S.F.	In all respects effects almost identical with those after intraventricular injection.					
Injection of 1.0 ccm. phenol-sulphonmethalein intraventricularly	Dye recovered from lumbar C.S.F. in 5 mins. and from urine in 20 mins.					
Warming the body	Flushing and sweating in all areas.					

Discussion.—Case 7 was an example of severe hydrocephalus, due to an extra-ventricular block. Absorption of the drug into the blood-stream from the ventricular fluid must have been so slow as to minimize the possibility of peripheral effects. The reaction to warming the body revealed the presence of some sweating centre in the central nervous system and proved the integrity of secretory fibres to the sweat glands of the face. The sweating response to pilocarpine injected subcutaneously or intravenously was not appreciably different from the normal. Intraventricular injection of a relatively large quantity of the drug had no effect of any kind.

Investigation of three other infants with hydrocephalus of approximately the same severity as that of Case 7 demonstrated that intraventricular injection might cause retching and vomiting, coughing, and, occasionally, slowing of the pulse, but no other effects were seen. When the drug was injected after withdrawal of as much ventricular fluid as could be obtained the result was the same. In all cases there was an apparently normal sweating response to subcutaneous or intravenous injection of the drug.

In these cases the block to the cerebrospinal fluid circulation was of such severity that pilocarpine introduced into the cerebral ventricle must have produced its effect by central action and not by peripheral action. The character of the responses indicated obviously a stimulation of medullary centres, and therefore the failure of the sweating response was not due to changes in the ependyma. Nor was the failure a result of dilution of the drug in excess of fluid since large quantities of the drug were employed and the response still failed after removal of excess fluid. The failure might, as Cushing suggested, be explained by destruction or functional impairment of a hypothalamic sweating centre. If this explanation be accepted, then, obviously, the sweating response, apparently normal in all, to subcutaneous injection of pilocarpine could not be due to an action of the drug on the centre.

Case 8 was an example of hydrocephalus of moderate degree where complete destruction or impairment of the centre was unlikely. The obstruction to the cerebrospinal fluid circulation was not great and peripheral effects were possible within twenty minutes. The responses to intraventricular pilocarpine, particularly flushing and sweating, were very similar in time relationships and character to those following subcutaneous injection, and were in fact such as might be expected from peripheral action of the drug after absorption into the blood-stream. A central action was probably the cause of the frequent vomiting, but the sweating response was neither so marked or prolonged as to suggest action on a sweating centre. Accepting Cushing's view of the response in normal adults, and assuming the presence of a hypothalamic sweating centre in young infants, we may explain the failure of central action in this case as due to partial impairment of the centre. Another possibility, however, is that such a centre is not developed in infancy, and that the sweating response observed was actually a result of peripheral action.

One other feature demands consideration. In all cases of hydrocephalus sweating occurred when the body was warmed, thus establishing

the presence of some sweating centre or centres in the brain or spinal cord. Intraventricular pilocarpine failed to stimulate the centres. If it is assumed that the centres are susceptible to the action of pilocarpine, it follows that the drug, when introduced into the ventricle, did not reach them. Possibly they are situated deeply in the substance of brain or cord.

Further speculation in this paper on the question of sweating centres in infants and adults is not desirable, as investigation on the subject is proceeding. The results so far obtained, however, furnish additional evidence that subcutaneous injection of pilocarpine causes sweating by peripheral action of the drug.

•
C.—Intradermal Injection of Pilocarpine.

The experiments in this section tested the view that pilocarpine acted on the sweat glands directly.

Methods.—The experiments were all conducted on one subject (Case 9). Injections were made in the skin of the back of the hands, which were previously warmed by immersion in water at 40° C. and then dried. Substances for injection were dissolved in normal saline solution, and 0.25 c.c. of the solution injected at a room temperature of 18° to 20° C. An intradermal wheal was first raised and the remaining solution injected at a slightly greater depth. In all experiments control injections of 0.25 c.c. of normal saline solution were made. The responses to different substances were compared by injecting at corresponding points on both hands. The duration of the sweating response was estimated by intermittent gentle and thorough drying of the area until the sweat beads failed to reappear. The skin temperature of the area was estimated. It was found that the activity of the sweat glands was approximately equal in all parts of the back of the hand.

The following substances were injected: Pilocarpine nitrate (0.25 to 2.5 mgm.), acetyl choline bromide (5 mgm.), eserine sulphate (0.1 mgm.), and histamine acid phosphate (0.1 mgm.).

Results.—Injection of all substances produced a local change very similar to the "triple response" which appears when the skin is pricked through a solution of histamine (Lewis, 1927). There was a central wheal and an encircling flare surrounded by a slowly invading halo. Injection was accompanied by a rise in skin temperature over the whole area, including the flare, and by pain of some severity but short duration, followed by a sensation of warmth locally. The skin temperature reached approximately the same level for all substances injected.

Normal saline injections produced a similar but less marked "triple response," and caused only slight discomfort.

The sweating response.—Sweating in the area of injection was produced by pilocarpine and acetyl choline but by no other substance. Normal saline solution produced no sweating. The "triple response" by itself was not responsible for sweating. When it was elicited by pricking the skin through solutions of each substance, no sweating was observed.

After injection of pilocarpine sweating appeared at between one and eight minutes and lasted up to one hour. It involved an area of skin which was roughly circular and about 2.5 to 3 cm. in diameter. The quantity secreted was small, and at its height the response showed merely as small beads just visible to the naked-eye, while frequently it could be determined only by examination with a magnifying lens. At the onset sweating tended to spread proximally in radiating lines, in a manner which suggested absorption of the drug along superficial lymphatics; later it became, like the flare, localized to the site of injection. Sweating persisted for some minutes after the flare had disappeared. Injection of eserine fifteen minutes previously did not augment the response as regards either quantity or duration. Atropine (0.1 mgm.) injected into the area caused cessation of sweating within two minutes.

The sweating response to acetyl choline was very similar to that of pilocarpine. The flare was usually more distinct and widespread. One notable difference was that the response was augmented by a previous injection of eserine, as illustrated by the following experiment.

Two areas were injected with eserine and two with normal saline solution. Fifteen minutes later acetyl choline was injected into one area containing eserine and into one area containing saline solution, and saline solution was injected into the remaining areas. No sweating occurred in areas containing saline alone, or saline and eserine. The response lasted for thirty-five minutes in the area containing acetyl choline and saline, and for fifty-five minutes in that containing acetyl choline and eserine, and in the latter area the quantity of sweat was appreciably greater. The response to acetyl choline was also stopped by local injection of atropine.

Discussion.—Sweating was not due to introduction of fluid, since saline did not produce it. Capillary dilatation, arteriolar dilatation, which was evidenced by the flare, and plasma exudation were not responsible, as these changes were well-marked in all injections and

especially after histamine. Similarly sweating was not solely a result of the rise in skin temperature. Eserine was employed to test for an indirect action of pilocarpine in producing acetyl choline by stimulation of cholinergic fibres. It is now established that acetyl choline is destroyed by a specific enzyme—an esterase—which is present in blood and other tissues, and that eserine acts by inhibiting the destructive action of the enzyme (Matthes, 1930). Eserine, as Dale expresses it, is an indicator of cholinergic effects. It is clear that in our experiments eserine prolonged and intensified the action of acetyl choline, but did not affect the response to pilocarpine. Thus pilocarpine did not act indirectly by stimulating cholinergic nerves.

We may conclude that sweating induced locally by intradermal injection of pilocarpine is a result of direct action of the drug on the sweat glands at the site of injection.

Two features observed in these experiments deserve special mention. The first is an apparent augmentation of the action of pilocarpine after absorption into the blood-stream. In the same subject the generalized sweating response to 15 mgm. of pilocarpine injected subcutaneously was compared with the local response to 2.5 mgm. injected intradermally on another occasion. The general response in the hands was not appreciably less than the local response, and sweating did not appear to be proportional to the calculated concentration of the drug in the tissues on each occasion.

Serum was tested and was found not to have any intensifying action. Pilocarpine dissolved in serum and injected ten minutes later had no greater effect than pilocarpine dissolved in saline.

Another factor tested was in increased circulating adrenaline. According to Cushny [9] there is evidence that pilocarpine induces secretion of adrenaline and Burn (1932) has shown that the effects of stimulating sympathetic vaso-dilator fibres are enhanced by increased adrenaline in the circulating blood. The possibility that sweat secretion could be similarly intensified was tested as follows.

At corresponding points on each hand pilocarpine was injected intradermally, an interval of ten minutes elapsing between injections. When sweating was well established in the first area and had just appeared in the second, 0.3 c.c. adrenaline was injected subcutaneously. The general effects of adrenaline on blood-pressure and pulse-rate were well marked. No obvious change was noted, however, in the sweating areas.

If, then, pilocarpine evokes a greater sweating response after absorp-

tion into the blood-stream, the augmentation is apparently not related to increased circulating adrenaline or to an action of serum. Probably the drug is more closely and accurately applied to the sweat glands by the blood than when introduced intradermally.

The second feature of note is the response to intradermal acetylcholine. Sweating lasted for thirty-five minutes after the introduction of 5 mgm. of the ester, and was intensified and prolonged to fifty-five minutes by eserine. The effect of eserine is evidence of the presence of the esterase, but the duration of sweating without eserine suggests that the quantity of esterase in the skin is not great, and that the ester is destroyed mainly after absorption into the blood-stream. Such a mechanism would permit of local cholinergic effects of considerable duration while protecting effectively against action on other organs or tissues.

II.—THE RESPONSES TO PILOCARPINE OTHER THAN SWEATING.

The actions of pilocarpine on the blood-pressure, heart-rate, skin temperature and secretions are illustrated in Charts A and B. These are records of the changes in Case 1, and in Case 9, a man of 36 years.

Flush and skin temperature changes.—The flush affected the "blush area," i.e. the face, neck and, to a lesser degree, the arms and front of chest. After subcutaneous injection it appeared at about the same time as did sweating, but usually faded before sweating ceased. It was accompanied by a rise of temperature of 1° to 2° C. in the skin of the face. The flush appeared after division of all types of nerves, and therefore was not due to a central vaso-dilator action. It was also present after degeneration of the nerves, though usually slight after sensory nerve degeneration, and, thus, was not solely a result of an axon-reflex. The probable cause was a direct action of the drug on the skin vessels. Burn (1925) found that pilocarpine in the cat exerted a dilator action which was confined to the capillaries. In man pilocarpine probably dilates the minute vessels of the skin.

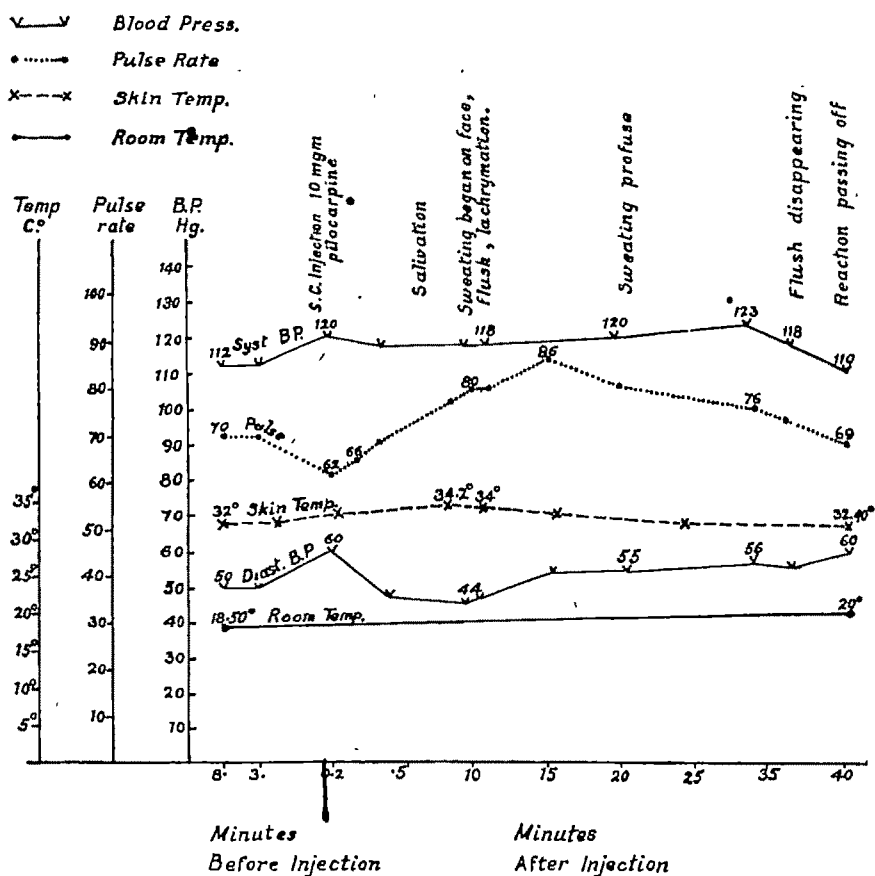
The flushing response to pilocarpine was compared with that to warming the body in normally innervated areas. The flush after warming the body was somewhat more vivid and associated with a greater rise in skin temperature. The greater rise in the skin temperature was clearly a consequence of increased blood temperature. After warming, the rectal temperature rose by 3° or 4° F., while no rise occurred after pilocarpine. Moreover, the skin temperature after

warming rose by 1° to 2° C. in desympathectomized areas which did not flush, and in which the vessels did not dilate.

It is of interest that the flush after pilocarpine has the same distribution as after intravenous injection of acetyl choline (Carmichael and Fraser, 1932).

Chart A.

Case 1. Male 11 Years.

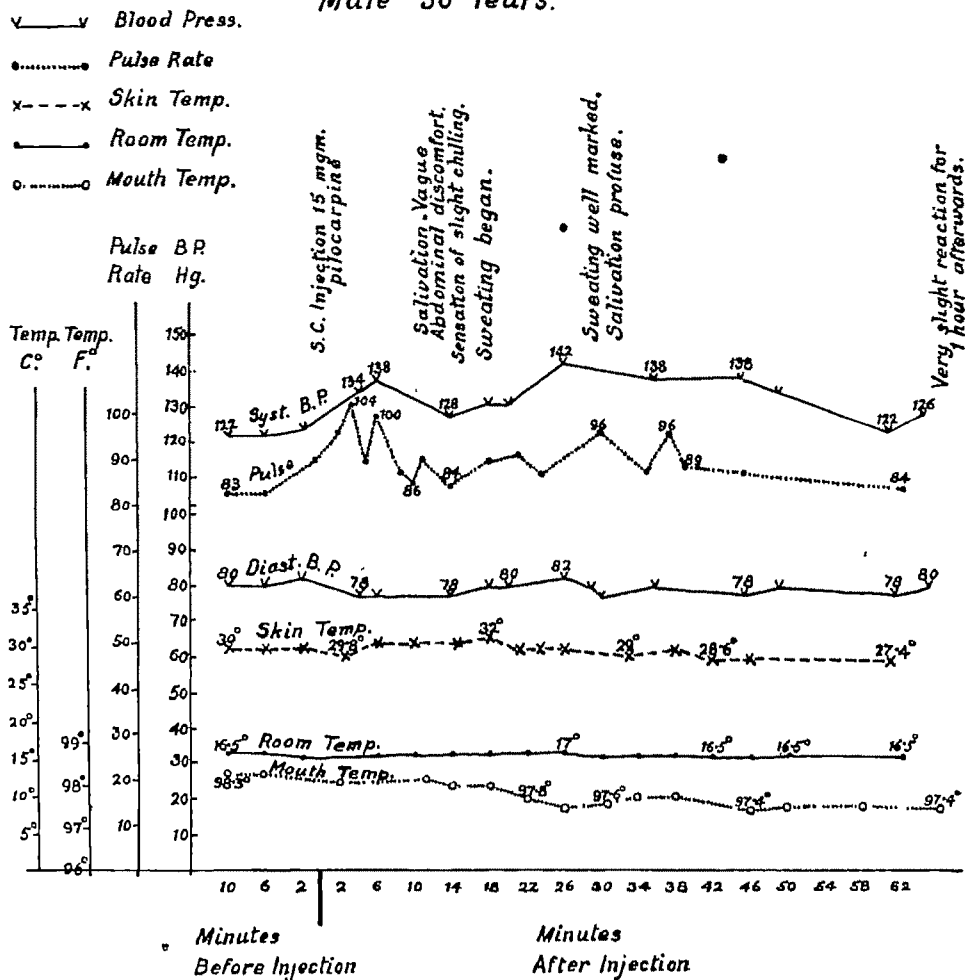


Heart-rate and blood-pressure.—The effect on heart-rate of subcutaneous injection of pilocarpine varied in different subjects. In three cases initial slowing was followed by an increased rate, while in six subjects acceleration was the only observable effect. In one case (Case 8) the heart-rate was slowed throughout; in Case 7 it was increased after subcutaneous injection and retarded after intravenous

injection. When acceleration was produced, the maximum rate was attained usually between ten and twenty minutes after subcutaneous injection. Acceleration was accompanied by a rise in systolic blood-pressure.

Chart B.
Case 9.

Male 36 Years.



Very similar variations have been described in the reactions of the human heart to acetyl choline injected intravenously. According to Carmichael and Fraser (1932) the usual effect was initial slowing followed by an increased rate, the first being accompanied by a fall,

the second by a rise in blood-pressure. Ellis and Weiss (1932, 1934), who administered the ester by continuous and prolonged intravenous injection, found that the heart-rate was generally unchanged or slightly increased, but occasionally retarded. The blood-pressure was unaffected or, in some subjects, moderately depressed. They found also (1934) very similar responses to acetyl- β -methyl choline, which, however, was 200 times as powerful as acetyl choline.

It is evident that the most constant effect on the heart-rate of pilocarpine or acetyl choline is acceleration, which is usually accompanied by a rise in blood-pressure. The obvious explanation of such effects of acetyl choline is the "nicotine-like" action on the suprarenal medulla, the fibres to which are cholinergic (Feldberg and Minz, 1933), causing secretion of adrenaline. In man this action is apparently shared by pilocarpine. Slowing of the pulse, which may precede quickening, is an example of a "parasympathetic" action.

It is possible, though improbable, that slowing of the heart-rate by subcutaneous pilocarpine was due to an action on medullary centres. Slowing occurred after intraventricular injection when peripheral effects could be practically excluded, but the concentration of the drug in the ventricular fluid was then much higher than could be offered to the brain centres by subcutaneous administration.

To summarize: the hæmodynamic effects on man of acetyl choline are a mixture of "nicotine-like" and "parasympathetic" actions, the former usually predominating. Those of pilocarpine are very similar, and possibly even identical.

Body temperature.—The fall in mouth or rectal temperature after subcutaneous injection was not greater than would be caused by the sweating produced.

Other actions of pilocarpine, such as salivation and lachrymation, have not been specially investigated.

III.—GENERAL SUMMARY AND DISCUSSION.

The investigations reported here demonstrate decisively that in man pilocarpine, introduced subcutaneously or intravenously, causes sweating by an action which is peripheral and on the sweat glands directly. Pilocarpine, therefore, acts on the sweat glands of man in the same way as on those of the cat. This evidence removes what appeared formerly to be an objection to the conclusion that the human sweat glands are supplied, like those of the cat, by sympathetic cholinergic fibres.

Some apparent differences between the action of pilocarpine in man and in the cat were also largely responsible for a belief that the sweat glands in man had a double innervation. In particular it was thought that in man pilocarpine acted on some fibres in the spinal nerves other than the sympathetic fibres. This view is now rendered untenable by the demonstration that pilocarpine sudorific action is not dependent on the presence of undegenerated nerve-fibres. Cushing, it is true, has suggested that the impulses to the sweat glands from the hypothalamic centre stimulated by intraventricular pituitrin or pilocarpine are propagated along sensory fibres with an antidromic action. The suggestion has still to be subjected to experimental test.

The hæmodynamic responses in man to pilocarpine and acetyl choline are evidently very similar, and the secretory responses are apparently identical. Indeed it is not improbable that a detailed study of the actions of acetyl choline and pilocarpine, when administered in the same way and in comparable quantities, would reveal even a closer convergence. The main difference is that acetyl chlorine, when injected subcutaneously, even with eserine, has no overt action on the heart, blood-vessels or secretions. Presumably it is hydrolysed immediately in the blood when it is absorbed slowly from the tissues.

Acetyl- β -methyl choline is apparently much less rapidly destroyed and is effective in men after intramuscular or subcutaneous injection (Starr, Elsom and Reisinger (1933). Its effects are very similar to those of pilocarpine similarly administered.

Pilocarpine, therefore, reproduces very closely all cholinergic effects in man. It does not, however, act by stimulation of cholinergic nerve-fibres. It acts directly on the sweat glands, on the blood-vessels and, probably, on all cells capable of response to acetyl choline. The exact mode of its action on the cell, like that of acetyl choline, remains to be determined.

CONCLUSIONS.

(1) In man the general secretion of sweat which follows subcutaneous injection of pilocarpine is due to peripheral action of the drug, and not to action on a hypothalamic sweating centre.

(2) Pilocarpine acts on the sweat glands directly and not through the medium of nerves or nerve-endings.

(3) The sudorific action of pilocarpine is, therefore, the same in men as in the cat. •

(4) These observations support the view that the human sweat

glands, like those of the cat, are supplied by cholinergic sympathetic fibres, and they furnish evidence against the belief that the human sweat glands have a double innervation.

(5) Changes in the sweating response to pilocarpine after nerve degeneration, the presence of sweating centres in the brain, and certain features of responses to intradermal injections of pilocarpine and acetylcholine have been discussed.

(6) Other actions of pilocarpine have been considered. The flushing response to pilocarpine is due to a direct action of the drug on the vessels of the skin, probably the minute vessels. Pilocarpine reproduces very closely cholinergic effects in man.

The majority of the patients in whom observations were made were under the charge of Mr. N. M. Dott. I am indebted to him for the opportunity of carrying out many of the investigations, and to Mr. A. B. Wallace for assistance in the experiments on intradermal injections.

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LOCALIZED ABNORMAL FLUSHING AND SWEATING ON EATING.¹

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THE literature contains not a few records of cases exhibiting, in limited areas of the head, flushing and sweating following eating. The explanation of such phenomena has been largely speculative owing to the difficulties in collecting data established by strict experiment. It has been our good fortune to see a case in which it was possible to determine further the mechanism of this abnormality by experimental means denied to previous observers and accessible to us in virtue of the unique site of the condition.

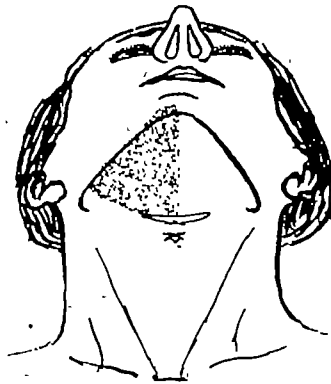


FIG. 1.

History.—E. G., female, aged 22.

When aged 5 the patient had glands in the right side of the neck removed through a horizontal incision over the middle of the sterno-cleido-mastoid muscle. No trouble was experienced until a year after the operation when, on eating, well-localized flushing occurred in the right submental region—a triangular area bounded medially by the mid-line, laterally by the ramus of the jaw to a point 1 cm. in front of the angle of the jaw, and posteriorly by the line of the hyoid bone (*see* fig. 1).

¹This work was done while Dr. Uprus held a Rockefeller Foundation Fellowship and Dr. Gaylor a Halley-Stewart Research Fellowship at the Neurological Research Unit, National Hospital, Queen Square, London.

Two years later, on eating, profuse sweating over the abnormal area made its appearance. The local perspiration was invariably initiated by flushing as a constant response to the stimulus of eating but frequently also with severe physical exercise. Apart from the condition in the neck the patient had enjoyed excellent health.

Examination.—The patient is a well-built healthy young woman, of high intelligence and thoroughly co-operative in the investigations to which she was submitted. On inspection under normal conditions, there was observed an area of light pigmentation in the right submental region. Over this area sensation to pin-prick and to cotton-wool was diminished; the "flare" response to scratch was present but was less extensive than, and not so persistent as, on the opposite and healthy side. Apart from these, no abnormal physical signs were detected on routine examination; sensation over the rest of the face was normal and the appreciation of pain, touch and taste over the whole of the tongue were intact. When the patient ate, flushing co-extensive with the pigmented and hypoalgesic region occurred after the lapse of a few seconds. Sweating was observed over the flushed area thirty to sixty seconds after the onset of flushing. On cessation of eating the flush at once began to fade and no more sweating was observed.

Examination of vasomotor reactions of abnormal area.—From this examination it was concluded that an abnormality of the vasomotor control and of the sweat secretion in the right submental region was present. The abnormal area was within the region supplied by the nervus cutaneus colli and the sensory disturbance indicated that this nerve had been injured, probably at the operation when the patient was 5 years old. The vasomotor supply to this region is from the cervical sympathetic, through the superior cervical ganglion to the second and third cervical roots from which the peripheral nerve is derived.

The first line of investigation was to examine the reactions of the abnormal area in response to stimuli calculated to cause fluctuations in the vascular calibre of the skin. In this laboratory the method of obtaining vascular responses and sweating following the application of heat or cold to the limbs has proved satisfactory in giving results constant within fairly wide limits. The legs were, therefore, immersed for twenty-one and a half minutes in a bath of water at 44° C., then transferred to a bath of water at 16.3° C. for twenty-six and three-quarter minutes. Flushing and paling of the skin were observed directly and superficial temperatures were recorded by means of thermo-couples. Sweating was assessed in degree and time by direct observation. In addition, the responses of the abnormal part to the stimulus of eating were observed under normal conditions and when general vaso-constriction in the skin as a whole with inhibition of sweat excretion was produced by cooling.

During the initial period of control which lasted twenty-four minutes, the patient was given an apple to eat. Before this the temperatures of the skin of the submental regions were within 0.2° C.; and on eating the apple a rise of temperature in the right submental was recorded within fifteen seconds, the

temperature of the opposite side remaining constant. Within two minutes the rise of temperature was 1.4°C . and about one minute after the commencement of flushing, sweating had established itself. After cessation of eating the temperature of the abnormal side fell 3.2°C ., or to 1.7°C . below that of the normal side and ultimately rose to the initial level. Sweating was observed for over a minute after the cessation of eating and disappeared before the temperature of the abnormal area had fallen below that of the normal side. When the stability of temperature recorded in the control period had been regained, the feet and legs were immersed in hot water. Flushing commenced in the normal submental region ten minutes after immersion of the legs into hot water and manifested itself on that side by a rise of a degree and a half. Only a very slight rise was noted in the abnormal side (*see fig. 2*). With the stimulus of heating the legs a minimal amount of sweating appeared on the abnormal side eight and a half minutes after the rise of temperature and sweating had declared themselves on the normal side.

Cooling by immersion of the legs in cold water produced an immediate fall in temperature and paling in the normal submental region; synchronously neither phenomenon appeared on the abnormal side. While the temperature of the normal submental region was continuing to fall, the patient was given an apple to eat. Similar effects to those recorded in the first part of this experiment were again noted, but the after-cooling was much more prolonged. Ultimately the temperature of the abnormal side rose above that of the normal side. It is to be noted that when vaso-constriction and inhibition of sweating were taking place in the rest of the skin, eating an apple produced the anomalous effects of flushing and sweating in the abnormal area.

Investigation of the affector mechanism.—From the history of the case eating an apple was indicated as being the most effective stimulus in causing the flushing and sweating, in the abnormal area. An analysis of affector stimuli was undertaken. Chips of apple laid on either side of the mouth did not produce the abnormal reaction, but immediately she commenced to chew flushing and sweating occurred. When the patient swallowed, apple chips being held in the mouth without chewing, only a slight momentary flush occurred. The stimulus of chewing with the left side of the mouth was as potent as that with the right. Mechanical stimuli, such as biting a stick, rubbing the inside of the cheek, gums and tongue with the finger did not produce the reaction. The routine testing of taste with salt, sugar, tartaric acid and quinine did not produce flushing when no movement of jaw or tongue was executed by the patient herself. 0.5 per cent. acetic acid held in the mouth produced a slight temporary flush with sweating fifty seconds later; swallowing the acid caused another flush.

Movements of chewing alone without any object in the mouth for a period of six minutes did not cause flushing. Chewing a wad of cotton-wool produced flushing in thirty seconds with some slight sweating. Chewing a wad of cotton-wool soaked in 0.5 per cent. acetic acid produced flushing in ten seconds and marked sweating.

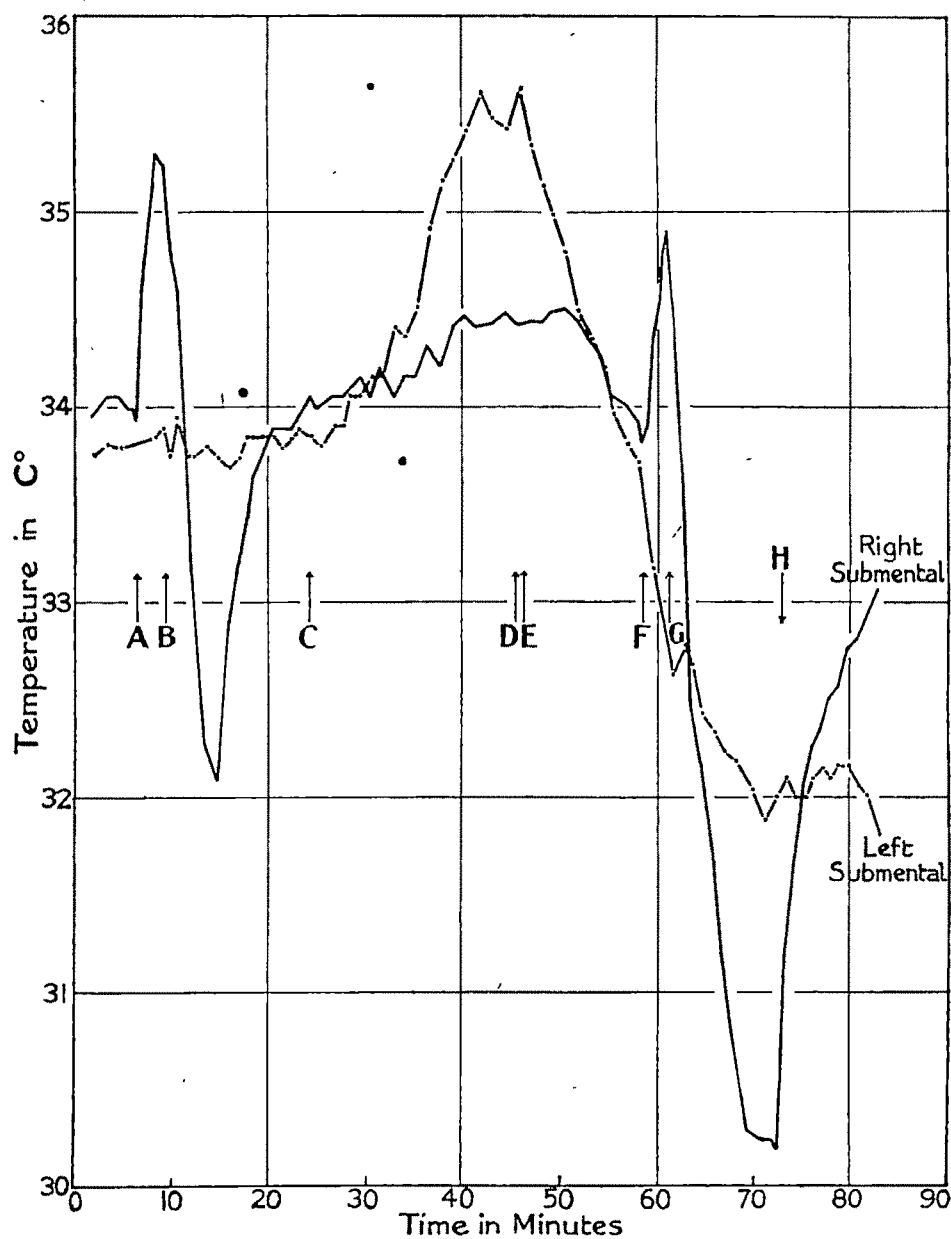


FIG. 2.—A, Commenced eating apple. B, Stopped eating. C, Feet into hot bath. D, Feet out of hot bath. E, Feet into cold bath. F, Commenced eating apple. G, Stopped eating. H, Feet out of cold bath.

The stimulus of smell proved ineffective and no reaction was noted following the inhalation of ammoniacal vapour through the nostrils. Movements of the scar and massage of the submaxillary region did not produce the abnormal reaction.

Anæsthetization of the right half of the tongue by painting its surface with 10 per cent. cocaine hydrochloride was carried out. Anæsthesia to pain and abolition of taste were established. The stimulus of eating an apple was again effective in producing the abnormal reaction.

Investigation of the effector mechanism.—The procedure here was of two kinds. Firstly, the effects of certain drugs with a known pharmacological action were tried, and secondly the effects produced by the anæsthetization of particular nerves.

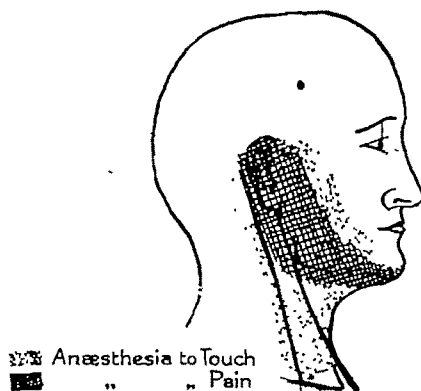


FIG. 3.

Five mgm. of acetylcholine were injected intravenously. A continuous record of the pulse was taken before, during and after injection. The cardiac rate was slowed, and flushing was observed following the injection and was general except in the abnormal area. The experiment was repeated with a larger dose (10 mgm.) with similar and more marked results.

In another experiment, 2 mgm. of atropine were injected subcutaneously. Within twelve minutes the pupils were observed to be larger and within fifteen minutes dryness of the mouth was experienced. At the end of twenty minutes the pulse-rate had risen from 60 to 120 per minute and five minutes later to 136 per minute. Twenty minutes after the injection she was given an apple to eat. Abnormal flushing, unaccompanied by sweating, occurred as an immediate response to the stimulus of eating: the flush did not pass off until three and a half hours later when the atropine effect on the cardiac rate was no longer evident.

Anæsthetization of the skin endings of the nervus cutaneus colli was accomplished by iontophoresis, using 10 per cent. cocaine hydrochloride for twelve minutes. The galvanic current caused so considerable a local histamine

reaction that it was considered advisable later to block the nerve as it emerges from under cover of the sterno-cleido-mastoid. This was done and the anæsthesia obtained showed that the great auricular nerve was also blocked (*see* fig. 3). Following the anæsthetization the abnormal area did not show the flushing, which was to be made out clearly in the distribution of the great auricular nerve and the normal position of the nervus cutaneus colli. At the height of anæsthesia the patient ate an apple; flushing and sweating occurred as under normal conditions.

The last procedure was to block the right lingual nerve with its chorda tympani component. The anæsthesia produced corresponded with the area innervated by the lingual nerve and the sense of taste was abolished on the anterior two-thirds of the tongue. There was suppression of the salivary secretion from the orifice of Wharton's duct of the right side. On being given an apple to eat there occurred no pathological response to the stimulus which under ordinary conditions always produced the effect.

CONCLUSIONS FROM EXPERIMENTAL WORK.

Taking as controls the responses of the skin of the face and the normal side of the chin when indifferent limbs were heated, the response of the abnormal area is definitely pathological. It behaved as does such an area to which the sympathetic outflow is defective; therefore not only have the sensory fibres running in the nervus cutaneus colli been interfered with, but also the sympathetic content of that nerve.

When the patient ate, flushing indicative of vaso-dilatation in the abnormal area occurred even when vaso-constriction was in progress. In the absence, therefore, of normal vasomotor and sudoral reactions to stimuli of heat and cold the behaviour of the abnormal region was independent of that mechanism responsible for body heat regulation. In short, the same stimulus which produced salivation caused a combination of vaso-dilator and secretory phenomena in the abnormal area of skin independent of general vasomotor activity.

The next line of investigation afforded more information about the nature of the affector stimulus. Mechanical stimulation of the old scar and of the region of the neck round about it was ineffective in producing the response. Mere mechanical irritation and mild taste in the mouth did not produce any effect on the abnormal skin. When chewing was commenced the effect was produced provided that there was something in the mouth. A strong taste of 0.5 per cent. acetic acid, without the movements of chewing and swallowing, was only slightly effective. The most intense reaction was obtained by eating an apple.

It is clear that the stronger the stimulus for salivation the more

readily did the abnormal skin reaction occur. From the fact that the reaction persisted after taste had been abolished on the homolateral side of the tongue, the mechanism was not likely to be a local one of the nature of an axon reflex from the taste endings to the periphery, but a reflex with an afferent pathway to the brain stem from either or both sides of the mouth.

Appropriate stimulation of one side of the mouth does not limit itself in effector response to the homolateral salivary glands but manifests itself in a general response on the part of the salivary glands of both sides. This section of the investigation definitely points to the affector stimuli being identical with those productive of salivation; lack of response on weak stimulation, such as passive movement and the use of small test quantities of various solutions placed on the tongue, may be considered as subminimal to the degree of stimulation required to produce the abnormal reaction or, on the other hand, the abnormal reaction may have been produced in so slight a degree as to have escaped detection by the means at our disposal.

The last part of the investigation was an attempt to establish the outgoing pathway. Acetylcholine given intravenously in doses sufficient to declare its physiological activity by slowing the rate of the heart caused subsequent vaso-dilatation in all regions except in the abnormal area. The transient activity of acetylcholine makes the interpretation difficult. It is known that a choline-like substance is liberated during activity of the submaxillary gland (Gibbs and Szelöczy, 1932), and that acetylcholine perfused through the gland is associated with glandular activity as estimated by the flow of saliva and the vaso-dilatation affected. Acetylcholine is very rapidly broken down by the presence of an esterase in the blood and consequently the cardiac manifestations occur first and may be the only evidence of its activity (Carmichael and Fraser, 1933). Two possibilities arose; the flushing may have been the result of peripheral activity of acetylcholine, or flushing may have been due to reflex vascular phenomena dependent upon the primary factor of cardiac inhibition. We believe that the latter explanation is the real one and that the peripheral vascular system responded as a whole to the cardiac inhibition; the abnormal area which has been shown to behave independent of general and indifferent stimuli did not respond. It was not considered possible to investigate this point further owing to the difficulty of obtaining a response on the part of the salivary glands to acetylcholine.

The effect of atropine pharmacologically on the salivary glands is to

render stimulation of the chorda tympani ineffective in causing secretion without impairing the vaso-dilator activity of that nerve. The result of eating during atropinization sufficient to inhibit salivary secretion was the production of a vivid vaso-dilatation in the abnormal area of skin without the usual accompaniment of sweating. This presumably is analogous to what occurred in the submaxillary gland at the same time. By eating the chorda tympani was stimulated; this nerve is known to have true vaso-dilator fibres as well as secretory fibres. Experimentally, on stimulation of the chorda tympani vaso-dilatation occurs in the atropinized submaxillary gland, but no secretion is poured out. In the present instance, the effector pathway was stimulated and vaso-dilatation, but no sweating, occurred in the abnormal area. Therefore, the outgoing pathways, the pathway to the submaxillary gland and the pathway to the skin are affected in precisely the same way by atropinization.

Anæsthetization of the abnormal area by blocking the nervus cutaneus colli was ineffective in stopping the abnormal reaction, as was suspected from the previous part of this investigation when the general vasomotor reactions were tested. It was concluded that the sympathetic outflow had been damaged and certainly the blocking of the nervus cutaneus colli confirmed this surmise, for the following reason. As a result of blocking a peripheral nerve the sympathetic constituents of that nerve are also blocked; following the removal of the sympathetic influence vaso-dilatation occurs in the peripheral distribution of that nerve; if the nerve be sectioned this same phenomenon occurs and persists for a long period until there is some development of intrinsic vascular "tone." Exactly similar phenomena are observed in pure sympathectomies. There is, however, an acute stage when sympathetic influence is removed. The great auricular nerve area and the area in the neck where sensation was intact showed vaso-dilatation in response to blocking the great auricular nerve and the nervus cutaneus colli, while that area where sensation was impaired remained unchanged until vaso-dilatation and sweating dependent upon eating were brought about. The abnormal area had lost its sympathetic supply and consequently blocking the pathway where that supply normally runs did not cause any alteration in the skin.

On anæsthetization of the lingual nerve with the chorda tympani the abnormal reaction of the vessels and sweating in the right submental region were not observed. The anæsthetization of afferent pathways might be invoked to explain the failure of this response, but we are

convinced that stimuli from either side of the mouth were equally effective and no difference in response was observed when half the tongue and the gums and cheek of the right side were cocaineized.

If it be granted, from the evidence that we have adduced, that there are, in spite of this homolateral anæsthetization, pathways through which effective afferent stimuli may travel, then the abolition of the vaso-dilator and sweating effect must be due to interference with the efferent pathway of the arc. The lingual nerve does not contain any efferent fibres other than those secretory and vaso-dilator fibres which come to it in virtue of its association with the chorda tympani. The efferent pathway would, therefore, appear to be in the chorda tympani. The chorda was involved by the anæsthetization since observation of the orifices of Wharton's ducts in the floor of the mouth showed profuse salivation from the left side and none from the right.

DISCUSSION.

We have been unable to find record of an identical case in a search through neurological literature. There are, however, two other conditions which appear to be closely related to the syndrome which has been described above. They are the auriculo-temporal syndrome and that of "crocodile tears." The symptoms of the former appear on eating, and are flushing and sweating in the distribution of the auriculo-temporal nerve. The ætiology of the condition in all the recorded cases is some suppurative process in or surgical interference with the parotid gland. The syndrome of "crocodile tears" is lachrymation occurring as a reflex response to eating. It is always consequent to facial paralysis, and in most authenticated cases the site of the lesion has been in the neighbourhood of the geniculate ganglion. It will be unnecessary to review the literature dealing with these two syndromes, but salient points from the literature will be cited in so far as they are germane to the subject.

Observers of these syndromes are unanimous that flushing and sweating in the auriculo-temporal syndrome and lachrymation in the "crocodile tears" syndrome are manifestations of the operation of a reflex arc, the afferent end of which is the gustatory ending. They are also agreed that the reflex is more evident with chewing some strongly tasting food. These points have been established in the present case.

To explain the origin of the reflex, various possibilities have to be considered.

Frey (1923) accepts the thesis that the reflex is essentially a normal

one but that it has become accentuated through injury to the auriculo-temporal nerve with subsequent irritation of vaso-dilator fibres in the cicatrix. André-Thomas (1927) invoked the idea of parareflexes to explain the phenomena. He cites as an example of a parareflex the excessive movement of the facial musculature in a recovering facial paralysis when the cornea is touched. There is, he says, no abnormality of the afferent pathway, but the efferent pathway has become unspecific in its activity. In this way does he explain the spread of the vaso-dilator effect from the parotid gland to the distribution of the great auricular nerve. Ford (1933) in his analysis of four cases of "crocodile tear" syndromes, gives a very similar explanation. Guttmann (1931), who published several cases of the auriculo-temporal syndrome, looks upon the condition as a release phenomenon. He claims that vaso-dilator and secretory fibres going to the affected area of the face are released from sympathetic control through the original trauma, and that those vaso-dilator and secretory fibres are activated by the stimulus of eating. In support of his argument he cites a case where on one side of the neck the cervical sympathetic with the superior middle and inferior ganglia had been extirpated along with the peri-carotid sympathetic network; on administration of pilocarpine sweating appeared first on the side of the face homolateral to the sympathectomy and later on the opposite side where it ultimately became greater in amount. From this observation he deduced that there are sweat fibres to the skin of the face apart from those derived from the cervical sympathetic.

Admitting the normality of lachrymal and skin reflex activity being set up by eating, Frey's view is difficult to accept since the formation of cicatrix *per se* is unlikely to heighten the activity of any reflex. The view that a parareflex operating through the nerve supplying the abnormal area is, so far as the present case is concerned, untenable since, if such were the mechanism, the anomalous response to the stimulus of eating would have been abolished by the anæsthetization of the nervus cutaneus colli. Guttmann's conception depends on the hypothesis that vaso-dilatation and sweat secretion in the skin of the face may be activated by nerves other than those derived from the cervical sympathetic. There is no established physiological or anatomical evidence to substantiate the claims that vaso-dilator fibres to the skin of the face exist, and that sweat secretory fibres occur in the cranial nerves apart from those sympathetic fibres of cervical origin.

In all cases with such abnormal flushing and sweating, injury has occurred to or in the vicinity of nerves which are known to contain true

vaso-dilator and secretory fibres. No similar syndrome has been recorded to our knowledge within the neighbourhood of a nerve which does not contain vaso-dilator fibres. It is probable that the presence of true vaso-dilator nerve fibres plays an integral part in all these conditions. From the above experimental work this is indeed so because with an anaesthetized chorda tympani and vaso-dilator impulses abolished, an invariably effective stimulus was applied without causing flushing and sweating. In the majority of the cases recorded in the literature there has been a long period of latency of some six to nine months to one or two years between the injury and the onset of symptoms. This lapse of time renders the possibility of a regenerative anomaly being the responsible factor.

In the present case the afferent pathway of this abnormal reflex has been identified with that of the salivary reflex, and the efferent pathway with the chorda tympani as far as the point where the nerve was blocked. The abnormal effect is related to activity in the chorda tympani. We have no evidence to connect the fibres of the chorda tympani with the vessels and sweat glands of the abnormal area, but the period of latency between the original trauma and the onset of symptoms is consistent with an unusual regenerative phenomenon having occurred.

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SPINAL TERMINATIONS OF THE PROJECTION FIBRES FROM THE MOTOR CORTEX OF PRIMATES.¹

BY E. C. HOFF,* D. PHIL., AND H. E. HOFF, D. PHIL.

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I.—INTRODUCTION.

THE course and terminal distribution of the pyramidal tracts has been studied in the past chiefly by Marchi's technique for staining myelin degeneration. Such degeneration from lesions of the motor cortex, or from interruption of the pyramidal tract itself, can readily be followed in the white matter, and some histologists have also succeeded in tracing it into the grey matter. However, a serious limitation of the method lies in the difficulty of observing the exact course of degenerated fibres after they enter the grey matter. Rothmann [31], for example, using the Marchi method in dogs and monkeys after pyramidal lesions, was unable to see degeneration in the grey matter of the cord even though degenerated fibres were clearly demonstrable in the dorso-lateral columns. As a result, he was led to suggest that the pyramidal fibres lose their myelin sheaths soon after they enter the grey matter. Later (1903) Collier and Buzzard [4] called attention to this possible source of error in the use of the Marchi method, since in their hands the technique was prone to leave unstained the distal portions of long degenerating neurones.

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Review of Literature.

In 1898 Pick [29] studied the problem in cats and monkeys through Nissl degeneration in spinal cord cells induced by prolonged faradic stimulation of the motor cortex. After stimulation of the arm area of the motor cortex for one-half to one hour, he removed pieces of the cervical enlargement of the cord. Nissl preparations of these pieces showed pronounced chromatolysis, not only in the large ventral horn cells, but also in neurones lying more dorsally in the grey matter. He decided, therefore, that these cells are intercalated neurones connecting corticospinal fibres with the ventral horn cells upon which the pyramidal tract eventually exerts its influence. Pick's conclusion was in essential agreement with earlier observations of von Monakow [27], who observed destruction of cells in the formatio reticularis and in the lateral horn of cats and rabbits after unilateral pyramidal lesions. At that time (1884) von Monakow called attention to two theories concerning the terminations of the corticospinal fibres: the first was that of Deiters [5], who believed that the pyramidal tract is interrupted in the formatio reticularis just caudal to the decussation of the pyramids, and that after all the fibres have come into contact with ganglion cells of this region the tract arises anew, so to speak, to proceed further caudally and to end gradually in the grey matter. Flechsig [7], on the other hand, denied any such relationship between pyramidal fibres and the ganglion cells of the formatio reticularis, believing that the tract proceeds without interruption into the cord, its fibres ending directly around the large motor nerve cells of the ventral horn. This direct relationship between the pyramidal fibres and the ventral horn cells was not shown by von Monakow, nor did he agree with Deiters' view that the lateral pyramidal tract arises from the formatio reticularis in the cord.

By examining Marchi preparations of the cords of monkeys sacrificed ten to forty days after unilateral extirpation of portions of the motor cortex, Mellus in 1899 [26] found it possible to trace degenerating fibres into the grey matter of the cord but none were found ending around ventral horn cells. In the same year Sharpey-Schafer [35] showed, after experimental lesions involving corticospinal fibres in cats and monkeys, that degenerated nerve fibres could be seen running from the pyramidal tract into the grey matter where they lost themselves as fine fibres amongst the cells of Clarke's column. He also was unable to follow pyramidal fibres into the ventral horn, nor could he demonstrate them in any part of the grey matter other than the base of the dorsal horn and Clarke's column.

Evidence that pyramidal tract fibres do end directly on ventral horn cells in the chimpanzee has been presented by Sherrington [9], and later by Leyton and Sherrington [22]. In their experiments, carefully circumscribed lesions of the hand area of the motor cortex resulted in a degeneration of small fibre filaments which could be traced in Marchi-Kulchitsky preparations into the ventral horn of the grey matter of the opposite side, especially in the lowest brachial segments of the cord. However, Lewandowsky in 1903 [21], using another modification of the Marchi technique, could see no degeneration of fibres in the ventral horn of monkeys after pyramidal lesions. According to his observations the corticospinal fibres end in the mid-region of the grey matter between the dorsal and ventral horns, from the formatio reticularis to the midline. In 1903 Rothmann [32] was able to confirm Lewandowsky's results on the monkey but still found it impossible to demonstrate with the Marchi method degenerated fibres in the grey matter of the spinal cord of cats.

In a study of myelin degeneration following lesions of the internal capsule in a monkey (*Macaca nemestrina*), Probst [30] detected fine, degenerated fibres in the contralateral grey matter of the cervical enlargement of the cord extending medially to about the middle of the base of the ventral horn and dorsally to the base of the dorsal horn. On the ipsilateral side similar degenerated fibres occurred very sparingly. Myelin degeneration was very scant in the grey matter of the thoracic and sacral segments but in the lumbar enlargements a degeneration similar in character and distribution to that in the cervical segments was observed. In another experiment, Probst called attention to the fact that the degeneration extended ventrally as far as the middle of the ventral horn. He could not confirm Sharpey-Schafer's observation that degenerated pyramidal fibres were to be traced into Clarke's columns.

In human cases of cord lesions involving the pyramidal tracts, Collier and Buzzard [4] prepared sections with the Marchi technique, and in two instances were able to see degenerated fibres running from the pyramidal tract into Clarke's column at the level of the tenth, eleventh, and especially twelfth thoracic segments. Moreover, they could not follow such fibres into any part of the anterior horn. In the succeeding year (1904), however, Dejerine and Dejerine [6] described Marchi preparations from a patient with a unilateral pyramidal lesion in which it was possible to follow degenerated fibres the entire length of the cord. In these sections they saw degeneration in both anterior horns; degenerated fibres were completely absent in the posterior horn.

Boutons Terminaux of the Pyramidal Tract.

This diversity of evidence concerning the final terminations of the pyramidal fibres seems to be largely attributable to the limitation of the methods used in tracing degenerating fibres, and it has, therefore, seemed advisable to re-investigate the problem with a technique that has been shown to reveal the exact termination of interrupted fibre tracts, namely, the method of Bouton degeneration. In preliminary experiments [15] the distribution of degenerated boutons terminaux in the cord of cats sacrificed three days after unilateral extirpation of the motor cortex showed that fibres from the destroyed area ended around ventral horn cells of the opposite side as well as cells lying further dorsally in the grey matter. Degenerated terminals also occurred on the ipsilateral side on cells in the ventral horn and the mid-region, but much more sparsely than on the crossed side. In an immature monkey (*Macaca mulatta*) investigated at that time, pyramidal endings were found in the ventral horn, but the majority of the terminals occurred in the region described by Lewandowsky, that is, in the grey matter of the intermediate zone. In the present studies, the distribution of the endings of cortico-spinal fibres from the motor cortex in adult monkeys and other primates has been determined by the same method.

(1) *Previous observations.*—In 1897 Held [10] demonstrated the existence of small loop-like structures occurring on the surfaces of neurones in the grey matter of the central nervous system. These Endfüsse or boutons terminaux, which were reported also in 1899 by Auerbach [1], again by Held in 1902 and 1904 [11, 12], by Cajal in 1908 and 1909 [2, 3] and later by others, have come to be recognized as axonal terminals forming synapses with other neurones. Inter-neuronal connections of this type have been seen in the spinal cord, medulla and brain stem; they occur on Purkinje cells of the cerebellum (Stóhr [36]), on cells of the granular layer of the cerebellum, as well as in the cerebral cortex (see, for example, Lorente de Nó [23]). They have been described in the rabbit, cat and dog, and occur also in the monkey [15], the baboon and the chimpanzee. Boutons terminaux essentially similar to those found in other mammals have recently been demonstrated in the human central nervous system [17]. Finally, there is evidence that such discontinuous synapses exist in lower animals as well. It has been possible to stain nerve terminals similar to boutons terminaux on spinal cord cells in the frog, and Sereni and Young [34] have shown that the mantle connective nerve of cephalopods ends by means of small terminal structure resembling mammalian boutons.

(2) *Bouton degeneration and its recognition*.—One of us [13, 14] has called attention to the fact that these terminal synapses rapidly undergo a characteristic degeneration after section of the axones of which they are the endings. This degenerative process can be seen in cats and monkeys as early as twenty-four to forty-three hours after the lesions as a swelling and thickening of the loops. After three days the boutons are enlarged granular masses which are readily distinguished from normal terminals. The degeneration proceeds to a complete disintegration of the boutons involved, in four to six days. These observations concerning the degeneration of boutons terminaux have been recently confirmed in monkeys by Foerster, Gagel and Sheehan [8] who sacrificed their animals three days after spinal de-afferentation. They also recognized the swelling and granulation characteristic of the degenerating synapse.

Sereni and Young [34] have also described degeneration of the small nerve terminals in cephalopods. After section of the mantle connective nerve, these endings become swollen and more deeply staining, and finally disappear completely in about two weeks. The time for total destruction of the terminals varies inversely with the temperature of the water in which the animals are kept.

Experimental modifications of the boutons terminaux, somewhat similar to their degeneration as a result of surgical lesions, has been described by Marinesco [24]. Cajal preparations of cords removed seventeen hours after ligation of the abdominal aorta in rabbits showed a modification of boutons terminaux in those levels which had been subjected to this experimental anaemia. Their form and volume were diverse, they were granular and sometimes very swollen and hypertrophied. Marinesco also observed [25] that boutons terminaux are sensitive to post-mortem changes. In dogs kept at room temperature for sixty hours after death, the boutons were greatly altered; their volume was diminished, they assumed irregular forms and they were very granular and vacuolated.

A similar post-mortem destruction of the boutons has been seen in the cat (E. C. Hoff [1932], unpublished observations). If pieces of spinal cord be removed aseptically and incubated for twenty-four hours in sterile physiological saline at 37° C. it is found that most of the boutons are destroyed, while those which remain are granular and irregular without showing the enlargement and destruction of the loop-structure typical of boutons degenerating as a result of nervous lesions in the living animal.

Post-mortem changes can thus be clearly distinguished from the degeneration following section of appropriate axones, and such degeneration of boutons may, therefore, be employed to determine the

distribution of the spinal endings of projection fibres from the motor cortex and from other levels of the central nervous system.

II.—RESULTS.

The present study is based upon an investigation of five animals: three macaques with unilateral extirpation of the motor area alone (Brodmann's area 4), and a baboon and a chimpanzee in which both the motor and pre-motor areas (Brodmann's area 4 and area 6) were removed on one side. All surgical procedures were carried out with the animals under sodium amytal or ether anaesthesia. Using aseptic technique an extensive bone-flap was turned back in each operation. The boundaries of the excitable area were in each case determined by monopolar faradic stimulation, and the tissue extirpated with care to to prevent damage to adjacent areas. Two to four days after the operation the animals were sacrificed by injection of a 10 per cent. solution of chloral hydrate, and histological material from the central nervous system prepared by Cajal's reduced silver method [14].

Unilateral Extirpation of Area 4.

Experiment 1.—*Mature male Macaca mulatta; weight 6,000 grm. (Pyramidal bouton series, No. 1.)*

The subject of this experiment had had the representation of the right lower limb removed from the left motor cortex on May 9, 1932 (see Schick [33], Experiment 21). On September 30, 1932, the animal was practically without evidence of motor deficit in the right lower extremity, and as any bouton degeneration resulting from that lesion would have completely disappeared, there was nothing to complicate its use for a three-day bouton experiment. The details of this operation and sacrifice are as follows:—

Operation.—On September 30, 1932, under sodium amytal anaesthesia, the right cerebral hemisphere was exposed and the lateral limit of the thumb area and the anterior boundary of the arm area accurately determined by monopolar faradic stimulation. There was a well-marked precentral sulcus which was taken as the anterior limit of the foot area, and the extirpation made accordingly. The central sulcus was carefully dissected away from the post-central convolutions and the entire block of tissue comprising the motor representation of the upper and lower extremities was removed in one piece (fig. 1).

The animal sustained a flaccid paresis of the upper and lower extremities of the left side which persisted until it was sacrificed.

Sacrifice.—On October 3, 1932, 2.15 p.m., seventy hours after the operation, the monkey was anesthetized with ether, and 1,000 c.c. of 10 per cent. solution of chloral hydrate in distilled water was injected into the brain and cord through the abdominal aorta, the arteries to the abdominal viscera and the brachial

arteries having been ligated. Injection was continued until clear fluid flowed from the opened inferior vena cava. The brain and cord were removed immediately and the latter was stained by Cajal's reduced silver method, formula 6a (Bolles Lee [20]). The blocks were dehydrated rapidly in alcohol, cleared in xylol, imbedded in paraffin, and serially sectioned at $15\ \mu$.

Distribution of degenerated boutons in the spinal cord. Experiment 1.—Upon examination, the whole series was found to be well impregnated; in the grey matter, the cell bodies and their dendrites were coloured purple to red-brown. Their nuclei had taken the stain sharply, and the intracellular neurofibrillar structure was clearly shown. Around the perikarya and dendrites, the pericellular neurofibrillar meshwork could be seen distinctly. Normal boutons terminaux and boutons de passage were present in large numbers as loop-like terminals of fine, darkly stained fibrils, densely applied to the cell bodies and the dendrites.

Not only were these normal terminals seen, but there were also present throughout the entire length of the cord on the side opposite the cortical lesion

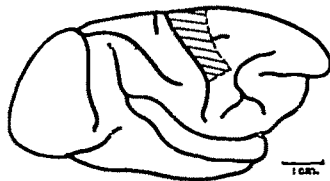


FIG. 1 (Experiment 1).—Right cerebral hemisphere, *Macaca mulatta*. The crossed-hatched area is the motor cortex which was extirpated.

enlarged, swollen and granular boutons on dendritic and perikaryal surfaces. On the uncrossed side, such degenerated endings were found also, although they were less numerous. In Plate XV, figs. 13 and 14, are shown degenerated boutons from this animal, at the level of the first and second segments, and for comparison Plate XV, fig. 15, shows degenerated boutons on an internuncial cell body in the seventh lumbar segment of an adult cat in which the 5th, 6th, 7th and 8th right post-thoracic dorsal roots had been sectioned extra-theccally three days before the animal was sacrificed. In each instance, the appearance of the boutons is essentially the same. As Plate XV, figs. 13 and 14 show, they are elongated, enlarged and granular, while the loops characteristic of the normal boutons can scarcely be distinguished. The shape of the degenerating boutons is variable, but for the most part they are long and spatulate or pear-shaped and thick. Usually they are twice or three times the size of average normal terminals.

The distribution of these degenerated endings, to which the term pyramidal boutons may be applied, is illustrated in the series of drawings shown in figs. 2, 3 and 4. In these figures the solid black circles indicate the position of perikarya upon which degenerated terminals occurred, the triangles represent

dendrites with such terminals, and the crosses indicate bouton degeneration on portions of dendrites so close to their cell bodies that their point of entry into perikarya could be seen in the section. The number of degenerated boutons on each cell body or dendrite is not shown in these diagrams. In fig. 5, however, the total number of degenerated terminals, irrespective of whether they were on cell bodies or dendrites, is indicated in drawings of the cord at the levels of the 6th cervical and the 5th post-thoracic segments. Each solid black circle represents 10 pyramidal boutons, and each drawing is compiled from three sections, indicating, therefore, the total number of degenerated boutons to be seen in a section of spinal cord 45μ thick. In such selected sections the proportion of pyramidal bouton concentrations in the uncrossed side to the crossed side was, in the cervical segment, about 3 to 7, in the thoracic segment about 1 to 3, and in the post-thoracic segment about 1 to 2.

At the first cervical level, pyramidal boutons occur chiefly in the intermediate zone lateral to the dorsal and ventral grey commissures. They were found also on ventral horn cells, but more sparsely. There are degenerated terminals on perikarya as well as dendrites, whereas in the young macaque previously reported [15] the pyramidal terminals were chiefly peridendritic. In the lower cervical segments, the distribution is similar to that at C1; degenerated boutons are predominant in the intermediate zone of the crossed side with many also on cells of the same region in the uncrossed side, and as in C1 a few on ventral horn cells.

In the thoracic segments, degeneration was restricted almost entirely to an area (x of fig. 3) just lateral to the central canal on the crossed side and the corresponding region on the side of the lesion. There were a few pyramidal boutons in the lateral horns, and some also in the ventral horn (fig. 3, Th. 6). Occasionally degenerated terminals were seen on cells of Clarke's column, but as fig. 3, Th. 4, shows, most of the degeneration occurred in an area just ventral and lateral to Clarke's cells.

The total number of degenerated boutons per section in the post-thoracic segments was less than in the cervical enlargement. They were distributed most densely in the intermediate region on both sides of the cord with only very few on ventral horn cells.

Experiment 2.—Immature male Macaca mulatta weighing 2,300 gm. (Pyramidal bouton series, No. 10).

Operation.—On February 1, 1934, under sodium amytal anaesthesia the left cerebral cortex was exposed and the excitable motor area (Area 4) delimited by exploration with a monopolar electrode. The whole of the motor area above the representation of the face was then removed in a single block (fig. 6a), using the cutting current of a Davis-Bovie unit to incise the arachnoid and a spatula to complete the extirpation (10.40 a.m.). Subsequent histological examination showed that the lesion, the anterior limit of which lay slightly in front of the line of excitable tissue, as determined by stimulation, had not, however, involved the premotor area.

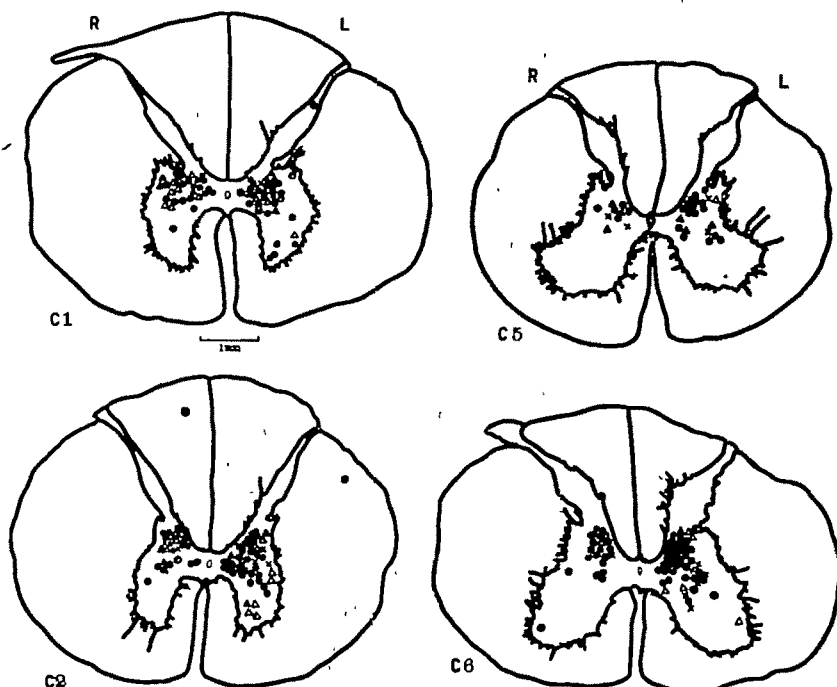


FIG. 2 (Experiment 1).—Sections from the cervical enlargement of the cord of an adult macaque sacrificed three days after extirpation of the right motor area. The solid black circles indicate the positions of cell bodies upon which degenerated boutons were seen. The triangles indicate dendrites showing such terminals. The crosses represent peridendritic degenerated boutons occurring close to the cell body. (Drawn with the aid of a projector.)

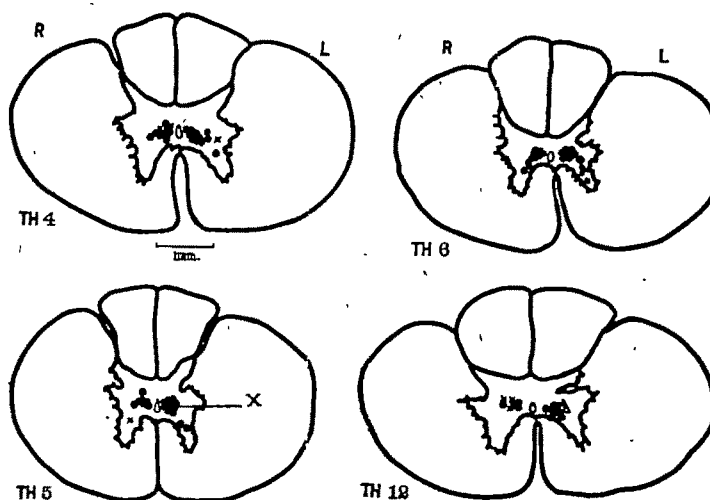


FIG. 3 (Experiment 1).—Sections from the thoracic region of the cord. The circles, triangles and crosses have the same significance as in fig. 2. (Drawn with the aid of a projector.)

Sacrifice.—On February 5, 1934, at 11.15 p.m., the monkey was anaesthetized and injected through the abdominal aorta with 500 c.c. of 0.9 per cent. saline, followed by 750 c.c. of 10 per cent. chloral hydrate. The brain and cord were then rapidly removed and placed for further fixation in 10 per cent. chloral hydrate. Segments of the cord were stained and sectioned.

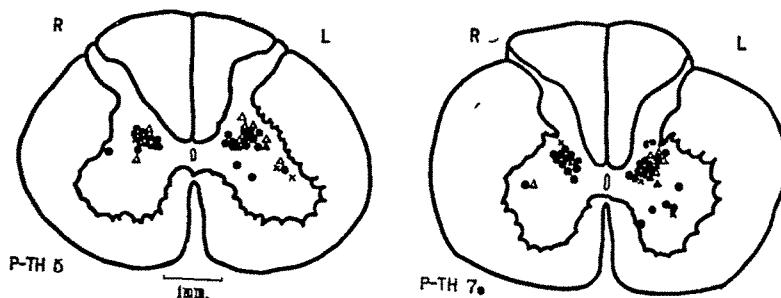


FIG. 4 (Experiment 1).—Sections from the lumbar enlargement of the cord of a macaque sacrificed three days after extirpation of the right motor cortex, showing the distribution of bouton degeneration. (Drawn with the aid of a projector.)

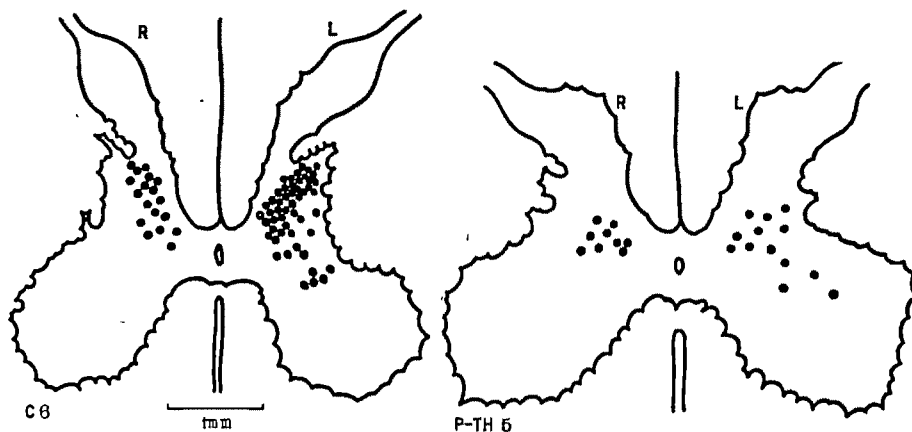


FIG. 5 (Experiment 1).—Drawings of the grey matter of the cord at the levels of the 6th cervical and 5th post-thoracic segments. Each solid black circle represents ten pyramidal boutons, and each drawing is compiled from three sections each 15μ thick.

Distribution of degenerated boutons in the cord (Experiment 2).—The sections were richly impregnated and of a translucent purple-brown colour, showing well-defined unshrunk nerve cells. Their nuclei and internal neurofibrils presented a normal appearance. Large numbers of boutons could be seen on the surfaces of cell bodies and the fine fibrils of which they were terminals could be traced for some distance from the cell. Most of the terminal fibrils were seen to approach the cell in this way, and did not form a thick fine meshwork such as is present in the cat [14]. Usually the fine fibrils ran along

the cell surface for 5 to 10 μ before they terminated, and often crossed other fibrils coursing along the cell surface. On the proximal parts of the dendrites, there were fine fibrils very closely applied to the dendritic surface. These fibrils sometimes crossed one another, but usually ran parallel. They terminated

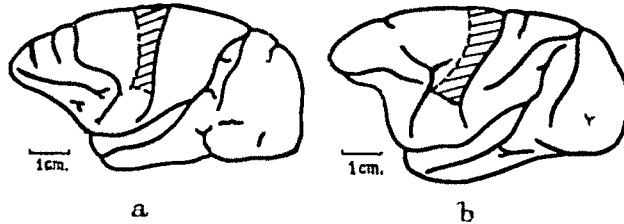


FIG. 6a (Experiment 2).—Left cerebral hemisphere, *Macaca mulatta*. The cross-hatched area is the motor cortex (above the representation of the face) which was extirpated.

FIG. 6b (Experiment 3) —Left cerebral hemisphere, *Macaca mulatta*. The broken line is the site of the superficial cortical incision made at the first operation and the cross-hatched area is the motor cortex which was subsequently removed.

by means of loop-like boutons in the same way as did the pericellular fibrils. The normal boutons of this preparation showed a striking correlation between size of the terminals and their distribution. It has previously been observed [14] in the cat that on the internuncial cells of the mid-region the terminal boutons

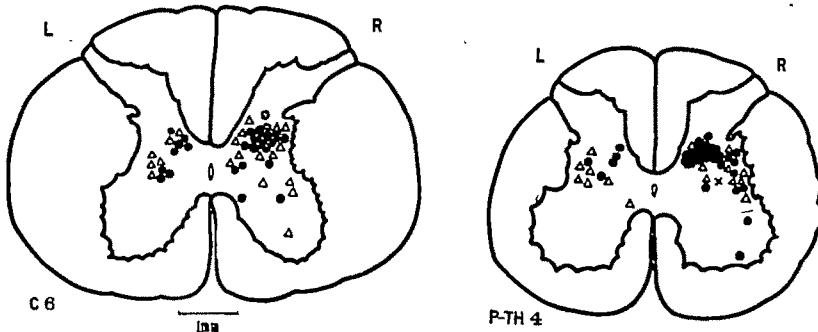


FIG. 7 (Experiment 2).—Sections of the cervical and lumbar enlargements of the cord of a macaque showing bouton degeneration after extirpation of the left motor cortex. The circle and triangles have the same significance as in fig. 2. (Drawn with the aid of a projector.)

are normally larger than ventral horn boutons. Not only are the largest boutons of the cells of this mid-region larger than the largest terminals of the motor horn cells, but the numbers of such large endings are also greater in the mid-region cells. In the present experiment, the normal boutons on the cells lying at the base of the dorsal and ventral horns were mostly of the large type. They were simple, round or elliptical loops without internal structure and in some cases greatly elongated and narrow. These large normal boutons

were found chiefly on the cell bodies. As had been seen previously in the cats, there was a large number of small boutons of the order of 1μ in diameter on the ventral horn cells. These minute loops were nearly always circular in shape.

The distribution of degenerated boutons is shown in fig. 7. In both the cervical and lumbar enlargements the most massive degeneration was present in a group of cell bodies and dendrites lying at the bases of the dorsal and ventral horns, and in the lateral and middle part of the ventral horn of the side opposite the lesion. In this animal there were only a few degenerated boutons on large ventral horn cells, and in many sections none could be found. The degeneration on the uncrossed side involved about a third as many boutons as that on the crossed side and occupied the base of the dorsal horn and the mid-region.

A remarkable feature of the distribution of the degenerated boutons on the cells of this cord is the fact that in the case of any particular cell they usually end exclusively on the dendrites with none on the cell body or vice versa. Thus, many cells could be seen with a particular dendrite studded with swollen terminals to within 2 or 3μ of the cell body proper, on which only normal boutons were present.

Experiment 3.—Immature female Macaca mulatta, weighing 3,200 grm. (Pyramidal bouton series, No. 7).

One of us has shown that in the monkey, fibres originating in the premotor area (Area 6 of Brodmann) sweep backward into the motor cortex and are thence projected uninterrupted into the cord. The present experiment has been devised to exclude the endings of these fibres in the bouton degeneration following extirpation of Area 4, and accordingly two operations have been carried out. First, a superficial incision separating Area 4 from Area 6 was made. Thirty-seven days later when the boutons constituting the terminals of the fibres from Area 6 had entirely disappeared the cortex was re-exposed and Area 4 extirpated.

First operation. Incision of cortex between Areas 4 and 6.—On January 9, 1934, the left cerebral cortex was laid bare under sodium amytal anaesthesia, and the line associated with the anterior margin of the Betz cell area identified. The vascular distribution of this region was such that an incision to a depth of 5 to 6 mm. was easily made, extending along the medial surface of the cortex to the cingulate and on the lateral surface down to the arcuate sulcus (fig. 6b).

The animal made a rapid recovery from the anaesthesia and on the same day showed a very slight paresis of the right upper limb with no weakness of the left side. This deficit on the right side became less and less noticeable, until the monkey's motor performance was practically normal two days after the operation. Ten days later there was no sign of deficit on either side. During the entire post-operative period, no forced grasping could be elicited nor was there any spasticity.

Second operation. Removal of motor area.—On February 15, 1934, using sodium amytal anaesthesia, the left-sided bone-flap made at the first operation

was re-elevated and the cortex explored with a monopolar electrode. Brisk, sustained, isolated responses in the face, arm and leg were obtainable on stimulation of appropriate regions of the motor area, but no motor responses could be evoked by stimulation of the cortex anterior to the incision made at the first operation. A block of tissue, including the arm and leg areas and extending anteriorly to the incision made on January 9, was extirpated in one piece about 6 mm. deep.

Following this operation, the monkey sustained a typical flaccid paresis of the right upper and lower limbs which persisted until it was sacrificed. By the third day there was a considerable recovery of the use of the right leg.

Sacrifice.—On February 18, 1934, the animal was anaesthetized with ether and injected with 1,000 c.c. of 0.9 per cent. saline. When clear fluid flowed from the opened inferior vena cava, 600 c.c. of 10 per cent. chloral hydrate were injected and the brain and cord were removed. Pieces of the cord were stained and sectioned at 15 μ .

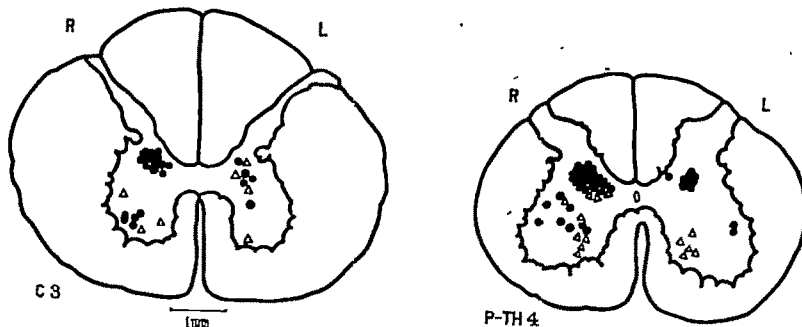


FIG. 8 (Experiment 3).—Sections from the cervical and lumbar enlargements of the cord of a macaque in which a superficial cortical incision between the motor and premotor areas was followed thirty-seven days later by extirpation of the left motor cortex. The solid circles and triangles represent cell bodies and dendrites upon which bouton degeneration occurred. (Drawn with the aid of a projector.)

Histological results. (a) *Extirpated block of cortical tissue.*—Examination of sections of the ablated motor area, stained by Nissl technique, showed a normal cortex with Betz cells of normal appearance. The line of the first incision lay chiefly slightly in front of the anterior limit of these cells although it had encroached upon the motor cortex about 1 mm. in the upper leg area.

(b) *Distribution of degenerated boutons in the cord.*—The bouton degeneration in this cord was considerably more circumscribed than in the previous experiments. Abnormal terminals occurred chiefly on the contralateral side on cell bodies which form a nucleus lying in the mid-region of the grey matter close to the medial boundary of the dorsal horn. Degenerated boutons were seen also on cell bodies and dendrites in the ventral horn, but while a majority or all of the boutons on the cells of the mid-region might be degenerated, there were usually only one to five of such degenerated endings on each of the

ventral horn cells. This was especially true of the large motor horn cells, which in many sections showed no degenerating boutons at all. The number of degenerated boutons on the uncrossed side was about one-third that on the contralateral side, and the terminals occurred on cells corresponding to those on which degenerated boutons were found on the crossed side. The distribution of cells showing bouton degeneration in this animal is illustrated in fig. 8 which is drawn from the third cervical segment and the fourth post-thoracic segment.

Unilateral Extirpation of Areas 4 and 6.

Experiment 4.—Aged female baboon (*Papio papio*) weighing 7,850 gm. (Pyramidal bouton series, No. 3.)

Operation.—On October 28, 1932, this old baboon was slow in its movements and definitely feeble in its reactions. However, the cortex was sufficiently excitable to permit definition of the boundaries of the motor area by means of monopolar faradization. After determination of the limits of left excitable area the motor and premotor areas were removed in one block. (See fig. 9.)

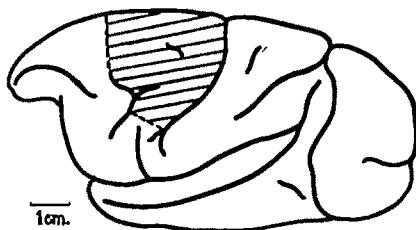


FIG. 9 (Experiment 4).—Left cerebral hemisphere of a baboon, *Papio papio*. The motor and premotor areas, cross-hatched in the drawing, were removed in one operation.

After this operation the animal exhibited a profound motor deficiency on the right side with no indication of return of voluntary movements up to the time of sacrifice. Forced grasping came on gradually until on the morning of the third day it was definitely present and sufficiently strong to support the animal's weight.

Sacrifice.—On October 31, 1932, under ether anaesthesia, 1,000 c.c. of 10 per cent. chloral hydrate solution were injected into the abdominal aorta, care having been taken to exclude fluid from the kidneys, stomach, and intestines by ligating all the arteries of these viscera. The brain and cord were removed at once and after further fixation pieces were stained as usual.

Histological results (Experiment 4). (a) *Extirpated cortical tissue.*—Examination of silver preparations of the cortical tissue removed at operation revealed in the motor area healthy, unshrunk neurones with centrally placed nuclei and well-stained intracellular neurofibrils. The extracellular fibrils formed a dense, rich meshwork in which the cell bodies lay. Boutons terminaux occurred on the perikaryal surfaces of the large pyramidal cells as well as on cells of other layers. Some of the smaller cells did not show synapses of the

terminal loop type. The premotor area presented essentially the same appearances: well-stained neurones lying in a thick meshwork of fibrils some of which terminated upon the cell bodies by means of boutons terminaux.

In the cord the extracellular neurofibrillar meshwork was very dense. In all regions of the grey matter the nerve cells themselves were unshrunk and the nuclei central in position. The internal neurofibrillar structure of most of the cells was normal in appearance, but in nearly every one of the large ventral horn cells the neurofibrils were destroyed in a circumscribed region, lying on one side of the nucleus, occupying as much as one-third the volume of the cell body.

(b) *Distribution of degenerated boutons in the cord.*—At all levels of the cord there were fewer boutons terminaux than in young adult monkeys. The normal terminals were simple loops with the smaller endings predominating. As in the preceding experiments, granular, degenerated terminals were found on both sides of the cord. On the side opposite the lesion these degenerated

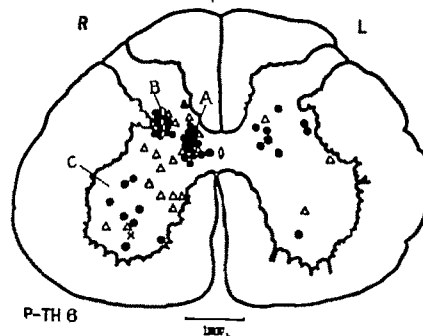


FIG. 10 (Experiment 4).—A section at the level of the 6th post-thoracic segment of the cord of a baboon sacrificed three days after extirpation of the left motor and premotor areas. The circles, triangles and crosses have the same significance as in fig. 2. (Drawn with the aid of a projector.)

boutons were distributed on cells lying in three groups: The first group included cell bodies and dendrites appearing in sections as a triangular area just lateral and dorsal to the dorsal commissure (fig. 10A). The base of this triangle lay opposite the central canal and the apex extended into the dorsal horn close to the medial border of the grey matter of the horn. The second group (fig. 10B) was located at the base of the dorsal horn lateral and dorsal to the first group; as seen in the sections, it is roughly circular in form. In this group degenerated boutons were seen on cell bodies as well as dendrites. The third group (fig. 10C) included cells and dendrites evenly scattered over the entire ventral horn. The number of degenerated boutons in this group was less than in either of the other two. Some swollen, granular endings were seen on the large ventral motor neurones.

Relatively little degeneration was found on the uncrossed sides, the ratio of the total number of degenerated boutons on the crossed and uncrossed sides

being approximately 4 to 1. Most of the degenerated terminals on the uncrossed side occurred in mid-region although a few were seen on ventral horn cells as well.

Experiment 5.—*Mature female chimpanzee; weight 33,000 gm. (Pyramidal bouton Series, No. 4.)*

This mature chimpanzee, about 13 years old, had not previously been operated upon. It used its upper extremities normally, but limped noticeably and showed an obvious weakness of the right leg and a tendency at times to lift the right thigh with the right hand as if to spare the leg from bearing weight. Examination showed that there was some atrophy of all muscles of the right leg, particularly of the muscles of the right hallux. The performance of the left lower limb was essentially normal.

Operation.—On March 11, 1933, the animal was anesthetized with ether and an extensive left-sided bone-flap comprising nearly the whole calvarium was turned back and the left hemisphere exposed by reflection of the dura medially. Monopolar faradic stimulation of the motor cortex elicited charac-

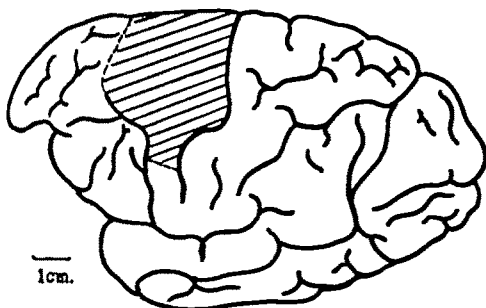


FIG. 11 (Experiment 5).—Left cerebral hemisphere of a mature chimpanzee. The cross-hatched area indicates the motor and premotor areas which were removed in one operation.

teristic sustained responses in isolated groups of muscles. From the leg area, extension and flexion of the right digits and ankle were obtained; in those movements, however, the hallux was not observed to move at any time. Flexion and extension of the wrist and digits of the contralateral upper extremity were elicited on stimulation of the arm area. These movements, like those in the lower extremity, occurred with very little latency and consisted of sustained responses of small groups of muscles, primarily in the distal parts of the limb. Stimulation of the premotor cortex gave rise to complex movements in both arm and leg of the opposite side. These responses, occurring after a period of latency as long as ten seconds, were slow movements of abduction, flexion, extension and rotation of several joints, particularly the shoulder and elbow, and the hip and knee.

After responses had been obtained from the motor and premotor cortex, a superficial incision was made between Areas 4 and 6. Following this incision, the motor cortex retained its previous excitability, but the sustained responses of the premotor area were abolished.

At 12.45 p.m. the motor and premotor areas were lightly coagulated at the margins with the cutting current of the Davis-Bovie unit and the entire block of tissue dissected out with a spatula and removed in one piece (see fig. 11). No responses of any sort could be obtained on subsequent stimulation of the crater of the lesion. The bone-flap was replaced and closure carried out. At the end of the operation 2 c.c. of Dial (Ciba) were given intraperitoneally; this kept the animal relaxed and quiet until the next morning when two further doses of 5 c.c. each were given.

Sacrifice.—On March 13, 1933, 5 p.m., anaesthesia was deepened by the intraperitoneal injection of 5 c.c. of sodium amytal, and 3 litres of 0.9 per cent. saline forced into the abdominal aorta. When the fluid flowing from the opened inferior vena cava was quite clear, 2 litres of 10 per cent. chloral hydrate were injected into the abdominal aorta and 500 c.c. into the right common

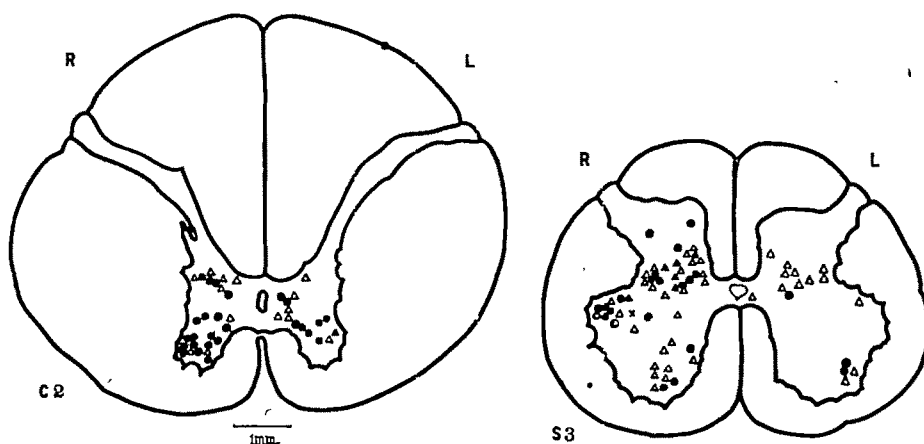


FIG. 12 (Experiment 5).—Section of the cord of a chimpanzee at the levels of the 2nd cervical and 3rd sacral segments showing the distribution of cell bodies and dendrites upon which bouton degeneration occurred after ablation of the motor and premotor areas. (Drawn with the aid of a projector.)

carotid in the direction of the brain. The brain and cord were removed and pieces of the cord impregnated and sectioned in the usual way.

Histological results (Experiment 5). (a) *Left motor and premotor cortex.*—Sample sections from the block of tissue extirpated at autopsy were prepared by the Nissl technique. The Betz cells in the arm and leg areas and on the medial surface of the hemispheres showed distinct anoxal chromatolysis. They were pale and somewhat swollen, the tigroid bodies were largely disintegrated and the nuclei eccentric, usually displaced to the side of the cell opposite to the point of exit of the axone. This chromatolysis was most severe in the lower leg and upper arm areas, although many normal Betz cells could be seen as well. In the face area, there was only an occasional degenerated Betz cell. The cells of Area 6 did not show the degenerative changes seen in Area 4. However, in a few cells, simple chromatolytic changes could be distinguished.



FIG. 13

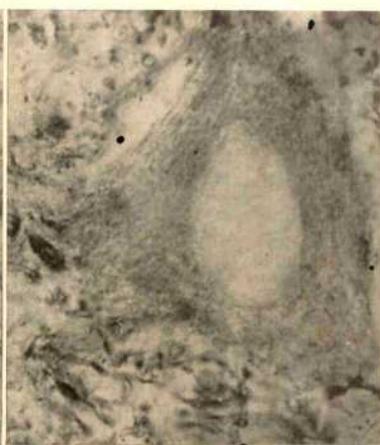


FIG. 14

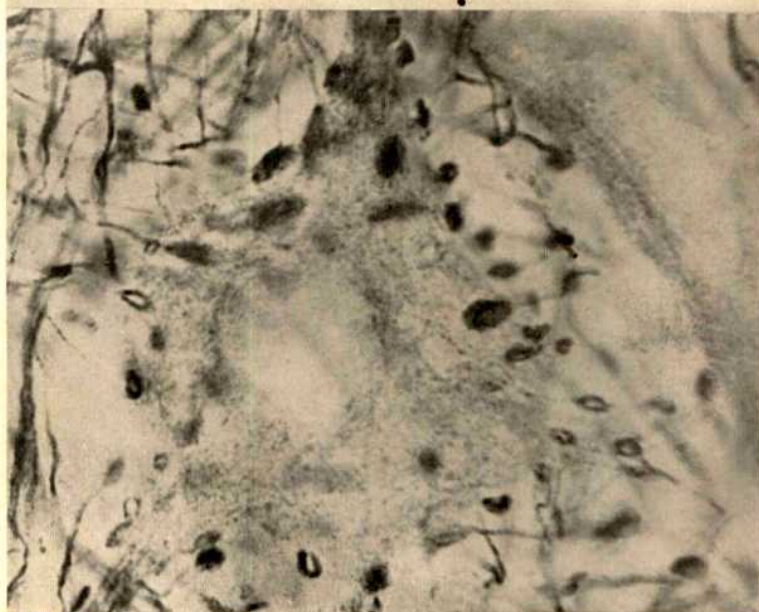


FIG. 15

FIG. 13 (Experiment 1).—Several normal boutons terminaux on the proximal end of a dendrite and the cell body of a neurone lying in the mid-region of the first cervical segment of the cord. On the right is a long fibril terminating in a degenerated bouton. Magnification: 1,600 diameters.

FIG. 14 (Experiment 1).—A cell at the base of the ventral horn in the second cervical segment of the cord. The microscope has been focused on a long, spatulate, degenerated bouton in the left of the figure. Magnification: 1,600 diameters.

FIG. 15.—A cell body lying in the mid-region of the grey matter of the 6th post-thoracic segment of the cord of a cat sacrificed three days after section of the right 5th, 6th and 7th post-thoracic dorsal roots. The photograph shows several enlarged degenerated boutons, as well as a number of normal terminals. Magnification: 2,000 diameters.

(b) *Distribution of degenerated boutons.*—The grey matter of the cord was well impregnated. The cell bodies were shrunken somewhat and showed definitely fewer boutons than did cells in the cords of the young adult animals. In general appearance and in synaptic structure and concentration these sections show striking similarity to corresponding preparations from the spinal cords of aged human patients with severe motor deficits [16]. The normal boutons stained darkly and appeared to be firmly attached to the cell bodies and dendrites. Thus, in instances where the cells had shrunk away from the surrounding fibrils, the boutons were generally still adherent to the cell.

The distribution of degenerated boutons is illustrated in fig. 12 drawn from the second cervical segment and the third sacral segment. In the cervical enlargement, degeneration was found on the contralateral side in the mid-region and in the ventral horn. There were degenerated boutons on cells in the ventral part of the ventral horn, especially in the laterally lying group of cells in the ventral-most region of the horn. On the ipsilateral side of the cord the distribution of degenerated boutons was very nearly the same as on the crossed side except that the degenerated boutons were fewer in number. The degenerated terminals were scarce in the lumbar enlargement, but in the sacral segments the degeneration again became more prominent. Cells and dendrites with degenerated terminals fell into three groups, lying (a) in the mid-region; (b) in the lateral horn; (c) in the ventral horn.

III.—DISCUSSION.

It may be seen from the foregoing experiments that restricted unilateral lesions of Area 4 are followed by bouton degeneration, which in the cord occurs for the most part in the intermediate zone or mid-region of the grey matter of the contralateral side. In adult animals, there is a greater spread of pyramidal boutons into the ventral horn than in young and immature subjects, as can be seen by comparing fig. 2 with fig. 7. Nevertheless, it should be concluded on the basis of all the experiments that the pyramidal tracts end chiefly around internuncial cells. In Experiment 3, in which the degeneration in the cord most nearly represents the termination of fibres originating in Area 4 only, pyramidal boutons are even more noticeably restricted to circumscribed groups of cells in the mid-region and the base of the ventral horn.

That the pyramidal fibres are thus associated with the more dorsal part of the cord was suggested in 1908 by Ariëns Kappers [19], who called attention to the fact that collaterals from the afferent roots end in the formatio reticularis and in the grey matter medial to it, and concluded that corticospinal fibres terminate mainly on cells which are in direct contact with afferent fibres. • The present results confirm these conclusions, particularly since the distribution of bouton degeneration

after dorsal root sections in monkeys shows considerable overlap with the area occupied by pyramidal boutons.

These experiments suggest also that there is direct connection between the motor cortex and cells on the same side of the spinal cord. It is not possible to decide whether the degeneration on the uncrossed side represents the termination of fibres from the direct pyramidal tract alone, or whether fibres from the crossed pyramidal tract may also recross in the cord to end finally on the uncrossed side. Studies of the separate distribution of the endings of the crossed and uncrossed pyramidal tracts are now in progress.

In Experiments 4 and 5 it has been possible to trace the spinal distribution of fibres from both the motor and premotor areas. In the baboon, as in the monkeys, there is a predominant area of degeneration in the intermediate zone, but in addition to this the whole ventral horn is also "peppered" with degenerated boutons. This is even more obviously the case in the chimpanzee, where bouton degeneration was found on cells in the ventral horn, including motor neurones.

It has been mentioned that lesions of Area 4 also involve fibres originating in the premotor cortex which pass backwards and descend with fibres from the motor area. Thus, it has been shown [18] that superficial slits between Areas 4 and 6 which involve no damage to Betz cells result in a degeneration which can be traced into the cord. Extirpations of Area 6 alone also result in degeneration of fibres in the white matter and their terminal boutons in the cord. It may be concluded therefore that the premotor as well as the motor cortex contributes fibres to the pyramidal tracts.

IV.—SUMMARY.

(1) The method of bouton degeneration has been applied to the study of the spinal terminations of fibre-tracts originating in the excitable cortex of monkeys and one chimpanzee.

(2) Following unilateral extirpation of the motor cortex (Area 4 of Brodmann) alone, degenerated nerve endings were found in the cervical and lumbar enlargements on dendrites and cell bodies lying in the intermediate zone of the contralateral grey matter, and in the ventral horn. Fewer degenerated boutons were similarly distributed on the ipsilateral side. In the thoracic segments degeneration of boutons could be demonstrated on both sides of the cord chiefly around cells lying ventral and lateral to Clarke's column.

(3) Removal of the motor area after complete degeneration of pyramidal fibres from the premotor area (Area 6 of Brodmann) resulted in degeneration restricted mainly to cells in the mid-region of the grey matter on the contralateral side. Only a few degenerated boutons were present in the ventral horn or on the ipsilateral side.

(4) When both motor and premotor areas were removed in one operation, degeneration of boutons occurred mainly around cells in the mid-region and the base of the dorsal and ventral horns of the contralateral sides, but was also found on cells evenly distributed throughout the entire ventral horn of both sides. Some degenerated endings were found on motor neurones.

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ACOUSTIC VALUE OF THE SEVERAL COMPONENTS OF THE AUDITORY PATHWAY.¹

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INTRODUCTION.

IN order to determine the acoustic value of the various components of the auditory pathway and how much each part contributes to actual hearing, the following procedure was adopted.

The animal, a dog, is placed in a stock with the right forepaw resting on a metal grid which can be charged with electricity. A stimulus-tone (1,000 cycles) is sounded for two seconds, directly followed with a charge just strong enough to effect hasty withdrawal of the paw. The animal soon learns to flex the foreleg as soon as the tone begins, thereby avoiding the imminent shock [2]. It continues to react, even though the tone be made progressively weaker, until the threshold of audibility is reached. While the threshold is being determined, particular care is used to keep the conditioned flexion intact, thereby assuring a definite response by the animal every time it can hear the tone at all. By this method the auditory acuity of dogs has repeatedly been measured in this Laboratory with a precision and consistency (standard error seldom exceeding one decibel) fully equal to the performance of human subjects.

When the normal threshold has thus been determined over a period of several days, various portions of the acoustic pathway are successively rendered non-functional by surgical means and the residual acuity in each case again measured. In this way the loss which follows functional elimination of a particular component of the auditory pathway as well the degree of hearing still mediated by the remaining tracts, can be accurately determined.

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EXPERIMENTAL OBSERVATIONS.

I. *Acoustic value of the cortex.*—After the normal acuity of several dogs was known, the cortex of one hemisphere was in each case removed. The loss in acuity proved to be relatively slight, being from two to five decibels. It should be particularly noted that the degree of impairment was virtually identical for right and left hemispheres (Table I and fig. 1): Removal of the entire cortex, however, has far more substantial

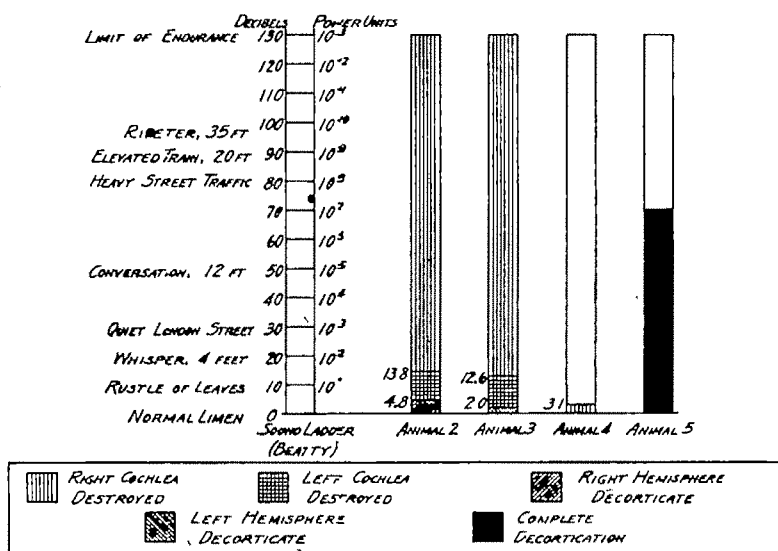


FIG. 1.—At the left the range of the (human) ear is represented as being 130 decibels from the faintest audible sound to the "limit of endurance." The "sound-ladder" (adapted from Beatty [1]) interprets these intensity-levels in terms of familiar sounds. The physical "power-units" rise from unity (10^0), which is just intense enough to be perceived by an average ear, to the gigantic figure of 10^{18} . Items 2 to 5 show graphically the facts of Table I for each dog separately. From these bars we see clearly how small a part of the total hearing-range is affected by elimination of one side of the cortex or one cochlea; and also how enormous is the loss due to ablation of the entire cortex. Even the decorticate dog, however, has about 60 decibels of residual hearing.

effects. Animal 5, after complete cortical ablation performed in four stages over a period of six months, was reconditioned and showed on the initial tests a consistent limen about 90 decibels above its normal level. As is customary in decorticate specimens, sensitivity increased until it seemed to be fairly stable at 70 or 75 decibels above normal. The magnitude of this impairment can best be appreciated in physical terms. The acoustic power which the dog was normally able to hear had, after decortication, to be multiplied 10,000,000 (10^7) times to evoke a response. Despite this huge loss, the decorticate animal still

possessed about 60 decibels of residual hearing. This limited degree of sensitivity is quite enough to enable it to get along fairly well in a world of heavy artillery, motor trucks and elevated trains.

II. *Acoustic value of the lateral lemnisci.*—Auditory impulses pass from the cochlea to the brain via the lateral lemnisci. Since each auditory nerve contributes to both lateral lemnisci, these tracts contain crossed as well as uncrossed fibres (fig. 2 (a)). In an animal from which

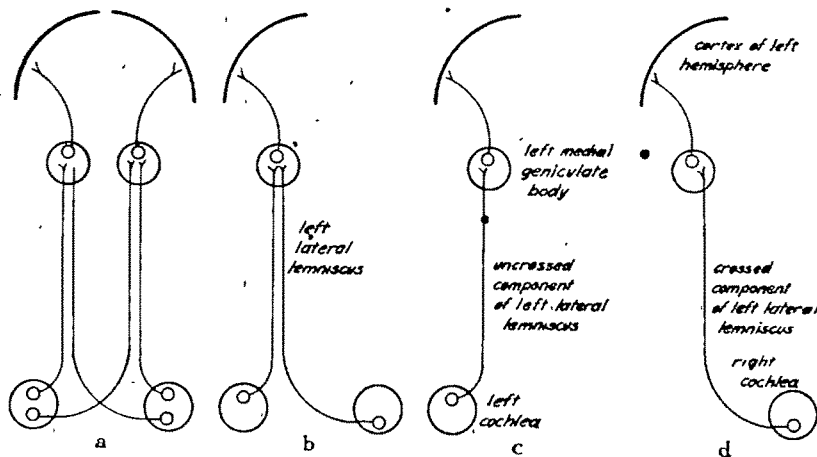


FIG. 2.—Diagram to show the distribution of the auditory pathways involved in these experiments. The intramedullary decussations are disregarded for convenience. (a) Situation in the intact animal showing the crossed and uncrossed components of the lateral lemnisci. (b) Functional pathways involved in an animal from which one hemisphere only has been removed. (The subcortical or geniculate end-station is disregarded on the right since the subcortical threshold is higher than the values tested in such an animal.) (c) Situation obtaining in an animal from which one hemisphere's cortex has been removed and the cochlea of the same side has been rendered non-functional. (d) The situation occurring when the cortex of one hemisphere has been ablated and the cochlea of the opposite side has been disrupted.

the cortex of one hemisphere has been removed the only cortical terminations remaining belong to the heterolateral lemniscus (fig. 2 (b)). We can thus measure the relative contribution of crossed and uncrossed components by destroying the appropriate cochlea in such an animal. If the right cortex be already ablated, destruction of the right cochlea will obviously create an additional drop in acuity, owing to functional lapse of the crossed (heterolateral) component of the left lemniscus (fig. 2 (c)). Destruction of the left cochlea will, on the contrary, be attended by functional deprivation of the uncrossed (homolateral) component of the left lemniscus (fig. 2 (d)). From Table I, animal 3, it will be seen that elimination of the *crossed* component of the remaining pathway in an animal from which the cortex of one hemisphere has

been removed occasions a hearing-loss of about ten decibels. Elimination of the *uncrossed* fibres (animal 2, Table I) likewise brings a drop of about ten decibels. While a loss of this magnitude constitutes an appreciable impairment of acuity for everyday sounds, a large amount of useful hearing still remains (fig. 1, columns 2 and 3) even though but a single one of the four main highways to the upper brain centres is still open.

TABLE I.¹

	Limen in decibels	Standard error of limen	Number
ANIMAL 2—			
1. Normal	0.0	0.76	4.5
2. First operation (right hemi-decortication) ..	4.8	—	1
3. Second operation (left cochlea destroyed) ..	13.8	—	1
4. Third operation (right cochlea destroyed) ..	*		
ANIMAL 3—			
1. Normal	0.0	0.84	8
2. First operation (left hemi-decortication)—			
First series	1.2	1.06	5
Second series	2.8	1.43	5
Mean	2.0	—	—
3. Second operation (left cochlea destroyed) ..	10.6	—	1
4. Third operation (re-entry on left cortex) ..	11.6	0.68	4
5. Fourth operation (re-entry on left ear) ..	12.6	0.00	8
6. Fifth operation (right cochlea destroyed) ..	†		
ANIMAL 4—			
1. Normal	0.0	1.26	9
2. First operation (right cochlea destroyed) ..	9.1	0.58	4
3. Second operation (left hemi-decortication) ..	‡		
ANIMAL 5—			
1. Normal	0.0	—	—
2. Complete decortication (four entries: 7.10.1933			
11.11.1933			
21. 1.1934			
15. 4.1934)			
Limen at 4.6.1934	ca. 90.0	—	2
Limen at 10.7.1934	ca. 70.0-75.0	—	4

* No response to pistol-shot within one foot of head.

† No response to pistol-shot within one foot of head, nor to tone 115 decibels louder than normal limen.

‡ No tests—animal succumbs to operation.

¹ A decibel is one-tenth bel. The bel may be defined thus: when the intensity of one sound (in physical units of sound-power or -pressure) is ten times that of another, the two are said to differ by one bel; when the physical ratio is 100:1, they differ by two bels, and so on. It will be noted that the standard error of most limens is less than one decibel; this indicates the precision of our measures. By "number" is meant the number of independent determinations of a given threshold; each one being based on 25 (or sometimes 20) separate records in the protocol. Each record, in doubtful cases, is derived from two or three actual responses by the animal. This care in arriving at the individual records helps to account for the low standard errors.

The normal limen is always set at 0.0. This does not mean that the four dogs start with identical acuity, but simply that all changes are measured from the subject's normal performance. The residual hearing after a given operation is therefore directly shown by its distance from the normal zero. In animal 2, we see that the first operation caused a loss of 4.8; which means that the stimulus-sound then had to be increased by 4.8 decibels over normal intensity before a response was evoked. After the second operation, hearing had been impaired by 13.8; the stimulus then had to be raised 13.8 to be just perceptible to the animal. These figures are reproduced graphically in the bar-diagrams of fig. 1.

III. *Acoustic value of the cochlea.*—In an animal otherwise intact, the temporal bulla of one ear was entered by ventral approach and the cochlea destroyed. A loss of three decibels followed (Table I, animal 4). Data from two cats, under test in another problem, may also be cited here. Both were tested at five frequencies (125, 500, 1,000, 2,000, 5,000 cycles) before and after complete destruction of the left cochlea. The mean loss of acuity at these five frequencies was 3.6 and 7.0 decibels. The cats being somewhat erratic in their performance, these figures are not so reliable as those from the dogs herein cited; but they do confirm the relatively small loss from elimination of a single cochlea. In order of magnitude it is seen that these observations agree, as might be expected, with the hemi-decorticate findings. Each cochlea serves one crossed and one uncrossed set of fibres; likewise the cortex of each hemisphere receives one crossed and one uncrossed component. In the case of cortical ablation, however, the sub-cortical centres still retain their connection with the cochlea and some degree of acoustic function, as indicated above (Table I, animal 5).

IV. *Analysis of the data.*—(1) The tests of hearing were conducted in accord with a well-established procedure, developed and standardized through a period of several years in this laboratory, by persons of long experience in handling animals. Full attention was given to repeated reinforcement of the conditioned response, to proper spacing of the tests, to keeping the animal quiet and composed, and to maintenance of uniform stimulus conditions.

(2) Only one test-frequency was used (1,000 cycles). This is an obvious limitation. It is conceivable that the relative distribution, in the crossed and uncrossed lemnisci, of the fibres which are involved in the animal's response to different frequencies may vary.

(3) Acoustic inequality of the two ears must also be considered. Inasmuch as no monaural tests were made, we cannot state the exact relative sensitivity of the two ears in a given animal; but certain inferences are possible. Let us assume the left ear, in a given case, to be distinctly inferior to the right ear. Destruction of the left cochlea should then reduce hearing but little below the animal's normal level. This we conclude from the results of animals 2 and 3. By ablation of one half the cortex, one crossed and one uncrossed pathway were both rendered almost wholly useless; and yet hearing was impaired only a few decibels. From this it seems reasonable to infer that loss of one poor ear could have but little effect. Destruction of the right cochlea, on the contrary, should induce a large drop, since all hearing would then

be mediated by the poorer ear alone. In all cases (except one to be examined directly) the loss was relatively small, hence we are constrained to infer that the destroyed ear could not have been appreciably superior to the remaining ear; it could only have been equal or inferior to the ear still in use. It should be stated that in no case was any middle-ear infection or gross abnormality noticed; the ears all appeared normal and free of pathological signs when entered. This, of course, gives no direct evidence about conditions within the cochlea.

(4) The subcortical centres (fig. 2*a*) acting alone (Table I, animal 5) do provide a modicum of hearing, or at least of functional response, to sound stimulation. Does this fact affect our conclusions in any way? In animal 5 (completely decorticate) the threshold of these infra-cortical centres proved to be 70 or 75 decibels above normal. In other words, the animal was quite deaf to ordinary sounds of moderate intensity. It seems clear then that these centres could not be responsible for the relatively acute sensitivity which persisted in animals 2 and 3 after unilateral decortication. It is hard to believe that centres, whose own limen is 70 decibels above normal, can be of any help in appreciating sounds which are only 15 decibels above normal. For this reason the sub-cortical centres are considered only in the wholly decorticate specimen.

TABLE II.

ANIMAL 1—				Lumen in cucubels	Standard error of lumen	Number
1.	Normal, first series	..	..	0.0	0.69	4
	Normal, second series	..	..	2.0	0.58	4
2.	First operation (right hemi-decortication)	..	..	0.0	0.50	2
3.	Second operation (right middle-ear waxed)	..	..	37.5	0.50	2
4.	Third operation (left middle-ear waxed)	..	..	58.5	—	1
5.	Fourth operation (left cochlea destroyed)	..	..	78.5	—	1

(5) One set of observations (Table II), not included in Table I or fig. 1, needs special interpretation. These figures, being obtained from a preliminary animal, reflect the absence of certain precautions used with the later dogs. In this case we find that removal of the cortex of one hemisphere reduces acuity not at all, even seems to raise it slightly. This cannot be accepted as correct. Being pressed for time, we tested this animal, particularly in the second series, as often as three periods daily; this may have fatigued him and reduced his normal score below its true value. We also note that elimination of the right middle ear was followed by an astonishing drop, 37.5 decibels; the corresponding figure from animal 3 (complete destruction of cochlea) is 10 decibels. These two figures, which should be almost equal, are quite

incomparable. The figures for animal 3, being derived from long and careful tests, are particularly dependable; they prove that a dog with but a single pathway (uncrossed) is able to hear within 13 decibels of its normal level. This being true, we can see no explanation for the huge loss in animal 1, save that the one remaining ear was defective. This is the only hypothesis which serves to clear up the anomaly. The one inferior ear would have no effect upon the limens of rows 1 and 2 (Table II), because the superior ear was still contributing; but when the good ear was waxed (row 3, Table II) hearing was mediated by the defective ear and then fell proportionably. Thirdly, we note some residual hearing after both ears had been entered and waxed. In this first animal we feared that breaking the cochleæ might induce vestibular symptoms of such magnitude as to make our tests unreliable, and therefore confined ourselves to opening the bulla, disarticulating the ossicles, and filling the tympanic cavity with heavy wax. This proved so ineffective for complete abolition of hearing that, in later animals, we resorted to actual fracture of the cochleæ.

In every case vestibular disturbances were thereby produced; but the major symptoms passed in a day or two, so that our tests were not appreciably hampered. This is well exemplified by dog 4 which, after losing one cochlea and displaying noticeable disturbances of vestibular function, tested perfectly and gave a threshold within three decibels of normal.

(6) In each case the operative intervention was carefully checked and the cortical removals verified. In animal 3, for example, the left hemisphere was removed. Upon autopsy it was found that in this animal all the cortex of the left hemisphere had been ablated. The site of the original tissue was occupied by a thick pad of fibrous tissue. The olfactory bulb and tract of the left side were intact. The left lateral geniculate had been somewhat invaded by fibrous connective tissue, and on the right a few sclerotic trabeculæ had invaded the medial side of the right hemisphere at the position of the sigmoid sulcus. Removal of these trabeculæ disclosed the fact that they occluded a sinus communicating with the third ventricle.

In order to verify complete destruction of one cochlea, the opposite cochlea was fractured in the same way and hearing again tested. Inasmuch as the animals then proved to be totally deaf to air-borne sounds (no response to pistol-shot within one foot of ears, nor to a 1,000-cycle tone whose power was 115 decibels above the normal limen), it is clear that the first cochlea had been adequately destroyed.

DISCUSSION.

In addition to the specific findings above mentioned, two more general conclusions emerge from this material. They are (1) the "factor of safety,"¹ which exists in the auditory system; and (2) the surprisingly significant role which the uncrossed fibres of the lateral lemniscus are capable of assuming in audition. The first of these is evidenced by the small hearing-loss which follows either removal of the cortex of one hemisphere or unilateral cochlear destruction (2 to 5 decibels). These two procedures deprive the organism of approximately one-half its normal acoustic equipment, one by abolishing the peripheral receptors, the other by removing the central termini; but this loss of 50 per cent. in neural mechanisms reduces the normal intensity-range of 130 decibels by only 2 or 3 per cent. This of itself tells us nothing, however, about the "safety-factor," which obviously depends on what we consider the "normal load" to be. If it can be shown to be of vital importance that the animal notice extremely faint sounds, so that even a loss of three decibels might impair its chances for survival, then the safety-factor becomes virtually negligible; whereas if the animal lives in an environment so protected that it can survive equally well by reacting to only the grosser sounds, then the safety factor may become quite large. If a loss of 13 decibels, when only one of the four major components of the auditory system continues operative, has no appreciable effect upon the animal's well-being, we may properly speak of a safety factor of 4 (more than Meltzer [5] had hoped for in nervous tissue).

We wish to stress the importance of recognizing that the uncrossed fibres of the lateral lemniscus have an acoustic value closely comparable to that of the crossed component. The significance of this fact is apparent when one recalls how often the acoustic is stated to be, chiefly if not entirely, a *crossed* pathway. Kreidl [4] clearly showed long ago that the uncrossed tracts of audition are significant for hearing. We cannot assert that precisely the same relations hold in the human as in the dog; but there again Kreidl found the situation for the primate to be very similar to that for the dog. In this connection, furthermore, it

¹ The term "factor of safety" may be defined as follows: Let x pounds be the breaking-stress of a steel cable whose cross-section is a . If the normal working-load which the cable must support is $x \div 10$ pounds, the factor of safety is clearly 10. But assume that the cable be composed of ten equal strands, any one of which alone can carry the normal load. The factor of safety is again 10. The second definition applies better to our acoustic situation than does the first.

should be noted that Dandy [3] reports no obvious impairment of hearing consequent upon removal of the right hemisphere in man. From this he inferred that the *right* hemisphere plays no significant role in audition. Although his evidence is somewhat invalidated by the chronic pathological nature of the cases prior to surgical intervention, it would appear that his results might be expected, not for the reason that the right hemisphere plays no part in hearing, but rather because of the physiological safety-factor and because of the important contribution of the uncrossed fibres.

SUMMARY.

(1) Removal of the cortex of a single hemisphere is followed by a drop in auditory acuity (at 1,000 cycles) of 2 to 5 decibels, a comparatively small loss.

(2) In a dog, at least, there is no appreciable difference between the right and left hemispheres in this regard.

(3) Removal of the entire cortex, however, produces an enormous reduction, from 70 to 75 decibels below normal levels.

(4) In animals with the cortex of one hemisphere removed, if the *crossed* fibres of the opposite lateral lemniscus be rendered non-functional, an additional drop in acuity of about 10 decibels is observed.

(5) In animals with the cortex of one hemisphere removed, if the *uncrossed* fibres of the opposite lateral lemniscus be rendered non-functional, there is likewise an additional loss in acuity of about 10 decibels.

(6) It follows that the uncrossed fibres of the auditory system are approximately equal in acoustic value to the crossed components.

(7) Destruction of one cochlea in an otherwise intact animal is followed by a loss of about 3 decibels. Destruction of both cochleæ produces total deafness to air-borne sounds.

(8) The physiological "safety-factor" in the auditory system thus seems to compare favourably with that observed in other organs of the body.

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SOME OBSERVATIONS ON THE CEREBRAL VEINS.

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THE details of the anatomy of the smaller veins in the body have, for the most part, but little interest. This is due to the extreme frequency of variations from the normal arrangement—indeed in some regions it is difficult to describe any particular arrangement as being the normal one. In the current descriptions of the superficial veins of the cerebrum it is found that while some points, such as the relationship of the vessels to the sulci and gyri of the cortex, are not mentioned, other details are always referred to. It is always emphasized that the posterior members of the superior cortical series of cerebral veins pour their blood into the superior sagittal sinus in a direction contrary to that of the blood flow in the sinus. In a similar way, mention of the superior and inferior anastomotic veins, connecting the superficial middle cerebral vein with the superior sagittal and transverse sinuses respectively, is made in most anatomical descriptions of the vessels. These statements point to the fact that the cortical veins have a more definite and constant arrangement than have most other veins of a similar size. The following investigation was undertaken in an endeavour to explain the course taken by the superior cortical veins of the cerebrum, and to determine the existence—or non-existence—of a constant relationship between the cortical veins and the sulci and gyri of the cerebral cortex. In the course of the work some points emerged relating to the anastomotic veins and the lacunæ laterales, and these will also be considered.

MATERIAL AND METHODS.

The cortical veins of the cerebrum were examined in five foetuses, whose ages ranged from six months to term. Before dissecting these specimens, the entire intracranial venous system was injected in the following way: both internal jugular veins were exposed and divided in the lower part of the neck; blood was removed from the vessels by irrigation with saline, and one vessel being clamped, a solution of indian

ink in 10 per cent. gelatin was injected until a pressure was reached which distended the intracranial veins without producing rupture of any one of them. Following removal of the skull, the dura was incised and the cerebrum injected at multiple points with a 5 per cent. formalin solution. The specimen was kept immersed in this solution for at least a week before dissection was commenced—a precaution necessary because of the extreme difficulty of hardening the foetal brain.

The vessels were next examined in ten adult dissecting-room subjects. In these the calvarium was removed with a minimum of injury to the underlying dura mater. This was now incised on each side of the middle line in such a way as to leave a median antero-posterior strip of the membrane $2\frac{1}{2}$ in. wide which contained between its two layers the superior sagittal sinus and the lacunæ laterales, and had attached to its inferior surface the falx cerebri. The remaining portions of the dura mater were removed, thus exposing the supero-lateral surface of each hemisphere with its covering of arachnoid and pia mater. In these specimens it was found that in most cases only the larger terminal portions of the superior cortical veins could be dissected with certainty, the smaller commencements of the vessels being collapsed and thin-walled and usually indistinguishable from the overlying leptomeninges. It is thought that this difficulty of examining the whole of the cortical veins in dissecting-room specimens may account for the present, and it is believed erroneous, description of the origin of the superior cortical veins. It was found that in many cases the whole extent of the cortical veins in the adult could be observed in fresh post-mortem brains in which these vessels are distended with blood.

The angles made by the terminal portions of the superior cortical veins with the superior sagittal sinus were measured as carefully as possible to the nearest 5° . In this connection it should be noted that each vein formed with the sinus two angles, one anterior to the vein and one posterior to it. The posterior angle was the one measured in each case. It should further be pointed out that while the measurements are accurate for the anterior veins which form large angles with the sinus, they are much less accurate for the obliquely running posterior veins which form relatively small angles with the sinus. For reasons which will be clear later, such inaccuracies do not affect the conclusions drawn from the direction of these vessels.

The superior sagittal sinuses of the foetal specimens were dissected. Transverse sections of these were examined with dissecting binoculars. The superior sagittal sinus and its lacunæ were dissected in the adult

specimens. A further series of specimens was obtained from the post-mortem room. Following removal of the calvarium, the falx cerebri and adjacent dura mater were excised. Bristles were passed into the cut ends of the larger superior cortical veins and the specimen pinned out on a board and dissected from its dorsal surface. The resulting specimens are illustrated in drawings, figs. 6, 7 and 8.

I.—THE CEREBRAL VEINS OF THE FŒTUS.

(a) *General arrangement.*—A general description of the cerebral veins as seen in the fœtus will first be given. In it will be included remarks on the origin, termination and number of the superior cerebral veins. The relationship of the vessels to the cortex and their direction will then be considered in greater detail.

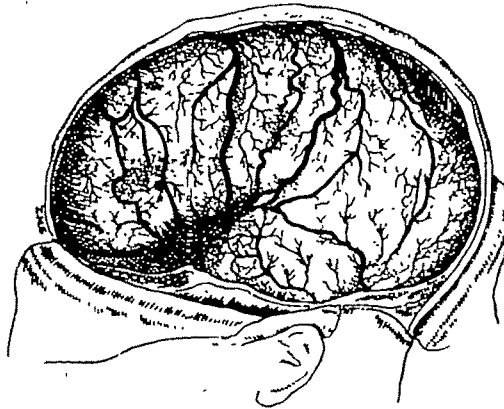


FIG. 1.—Drawing of specimen, showing cortical veins in a fœtus, aged 6 to 7 months, following injection of these vessels with a coloured gelatin solution. The radiation of veins from the region of the insula is well shown. The majority of the veins pass to the superior sagittal sinus, but two course postero-inferiorly to the transverse sinus.

A number of large veins radiate from the stem of the lateral fissure, in which region they unite to form a single trunk which drains either into the cavernous sinus or the sphenoparietal sinus at its medial end. Of these tributaries of the superficial middle cerebral vein, some (1-2) pass anteriorly in the direction of the frontal pole; others (5-6) pass superiorly, with varying degrees of obliquity, to supero-medial margin of the hemisphere; while the remainder (1-2) pass postero-inferiorly to the temporo-occipital region. Of the larger veins radiating from the stem of the lateral fissure (those enumerated) the majority, if not all, terminate by passing from the surface of the cerebrum into one of the

large venous sinuses—either superior sagittal or transverse. These facts are illustrated in the drawings of three of the dissections—figs. 1, 2 and 3. One of these (fig. 1) is from a foetus aged between 6 and 7 months; one (fig. 2) is from a foetus of 8 months; the other being from a foetus at term.

Turning now to a more detailed examination of the superior cortical veins: As regards their origin the larger veins of the group are all continuous with the tributaries of the superficial middle cerebral vein, as can be seen in the drawings. There are, however, also smaller vessels belonging to the superior series, and the details in connection with these could only be made out with the aid of dissecting binoculars. They are found to commence in a capillary zone about midway between the supero-medial margin of the hemisphere and the lateral fissure. It is important to note that small tributaries of the superficial middle

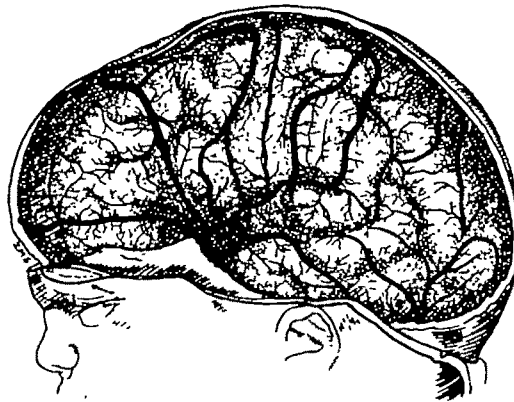


FIG. 2.—Drawing of specimen, showing cortical veins in a foetus, aged approximately 8 months. The radiation of the veins from the stem of the lateral fissure to the superior sagittal sinus is again clearly shown. Two veins (one incomplete) can be seen passing from the region of the insula to the transverse sinus.

cerebral vein also commence in this capillary zone and then pass inferiorly to join one of the larger vessels.

As the vessels are traced superiorly they increase in size and all terminate by entering the superior sagittal sinus. The larger vessels show slight dilatations before piercing the wall of the superior sagittal sinus. There being no *lacunæ laterales* in connection with this sinus in the foetus, the question of the relationship of vein to lacuna does not arise.

There is considerable variation in the number of superior cortical

veins present, not only in different specimens, but on opposite sides of the same specimen. This is shown in Table I.

TABLE I.

Specimen	Left hemisphere			Right hemisphere		
1	12 veins terminating in superior sagittal sinus			13 veins terminating in superior sagittal sinus		
2	14	"	"	8	"	"
3	8	"	"	8	"	"
4	8	"	"	7	"	"
5	8	"	"	5	"	"

The size of the vessels was found to be inversely proportional to their numbers. In both the adult and foetus eight veins were the commonest number present on each side, and also the average number

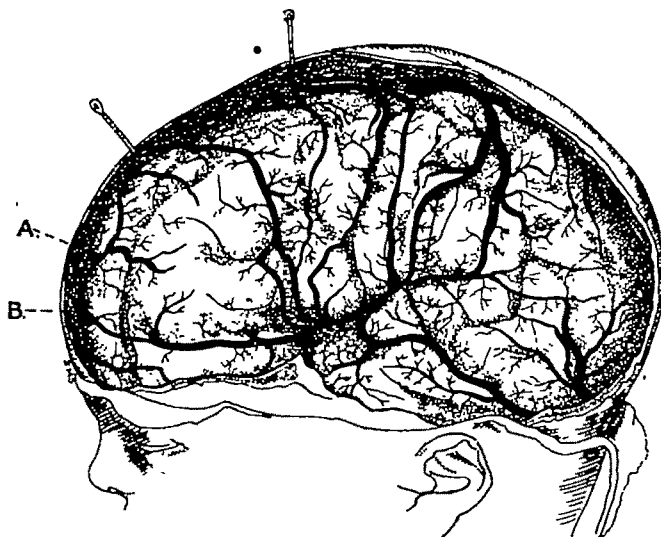


FIG. 3.—Drawing of a specimen, showing cortical veins in a foetus at term (a large infant). The radiation of vessels from the stem of the lateral fissure is seen—the majority passing to the superior sagittal sinus, but two to the transverse sinus. This specimen also shows that as regards their direction, the superior cortical veins are in two portions: (1) That radiating from the lateral fissure and (2) the terminal portion which changes its direction as it enters the sinus. A, Vein from medial surface of hemisphere passing anteriorly to unite with vein B immediately before it terminates in sinus.

for the series of foetal and adult specimens examined. It is of interest to note that wherever more than this number of veins was present there was a grouping of the vessels so that as many as three opened into the sagittal sinus at closely adjacent points.

(b) *The direction of the superior cortical veins.*—From the point of view of their direction the superior cortical veins of the cerebrum must

be considered in two parts. The inferior portions of these vessels, whether continuous or not with the tributaries of the superficial middle cerebral vein, radiate from the stem of the lateral fissure, like the spokes of a wheel, which has this point for its hub. * The second or terminal portions of the veins change their course and pass from the superomedial margin of the hemisphere into the superior sagittal sinus. These two portions of the veins are particularly well seen in fig. 3.

With regard to the direction of these terminal portions of the veins in the foetus, it is found that in the case of the anterior veins (1 or 2) they enter the superior sagittal sinus at right angles or with a very slight posterior inclination. In the case of the remaining veins, they are found to turn anteriorly and enter the sinus obliquely, the obliquity being best marked in the case of the most posterior veins. These points are illustrated in Table II. In this the posterior of the two angles made by the veins with the sinus is recorded, and the order in which the angles are set down from left to right corresponds to that of the veins on the cortex from frontal to occipital pole.

TABLE II.—SHOWING THE POSTERIOR ANGLES MADE BY SUPERIOR CORTICAL VEINS WITH THE SUPERIOR SAGITTAL SINUS AT THEIR POINT OF ENTRY INTO IT. THE SEQUENCE OF THE ANGLES FROM LEFT TO RIGHT CORRESPONDS TO THE ORDER OF THE VEINS FROM FRONTAL TO OCCIPITAL POLE. IN ALL CASES THE ANGLE MEASURED IS THAT WHICH IS DIRECTED ANTERIORLY AND IS THEREFORE OPEN POSTERIORLY.

Specimen	Side of hemisphere	Angle between terminal point of vein and superior sagittal sinus							
1 Foetus, aged 6-7 months	Left	90°;	90°;	120°;	70°;	55°;	45°;	40°;	40°
	Right	90°;	90°;	15°;	40°;	35°;	30°		
2 Foetus, aged approx. 8 months	Left	90°;	115°;	55°;	80°;	20°;	20°;	20°;	20°
	Right	90°;	45°;	45°;	25°;	20°;	10°;		
3 Foetus term	Left	90°;	90°;	85°;	70°;	40°;	40°;	30°	
	Right	90°;	90°;	75°;	50°*;	75°;	80°;	40°;	35°
4 Foetus term	Left	90°;	90°;	70°;	50°;	45°;	35°;	30°;	
	Right	90°;	80°;	70°;	50°;	50°;	40°;	30°	
5 Foetus term but very large	Left	100°;	90°;	50°;	45°;	40°;	25°;	20°	
	Right			90°;	75°;	35°;	30°;	25°	

* = Very small vessel.

(c) *The relationship of the veins to the gyri and sulci of the cerebrum.*—A constant relationship between the cortical veins and the more important sulci and fissures might have some surgical significance in facilitating the localization of these sulci. Such relationship, or its

absence, is not described in the current anatomical works. Sargent, in his description of these vessels, mentioned four main trunks, frontal, precentral, postcentral and occipital. He pointed out that these do not constantly lie in the fissures. From observation of the cortical veins in the injected foetus and in fresh post-mortem brains of adults, in which the cortical veins are often rendered very obvious by contained blood, it is considered that while the smaller veins are variable in position and numbers, the larger vessels have a constant relationship to the cortex in certain important regions.

Firstly, the relationship between the larger superior cerebral veins (those terminating by separate openings in the sagittal sinus) and the lobes of the cerebrum will be considered. In the specimens examined it was found that between three and six of the vessels had their origin on the cortex of the frontal lobe. The majority of these were small, but one or two were usually larger than the others. Three or more large veins passed from the surface of the parietal lobe to the sinus. In the majority of cases no vein was found passing from the occipital cortex to the sinus, although a vessel on the surface of the hemisphere in this region was always found passing forward to open into a large vein, constantly present in the lateral parieto-occipital fissure.

The relationship between the vessels and the more important sulci and fissures will now be considered. In the youngest of the specimens examined (six to seven months, approx.), the opercula of the insula are incompletely developed and the central sulcus shows itself as a widely open depression. None of the other sulci or fissures is present at this stage. The tributaries of the superficial middle cerebral vein can be seen, as has already been described, radiating to the superior sagittal sinus and to the transverse sinus in regular sequence. They have, of course, no relationship to the fissures which are as yet undeveloped. In all the other specimens the sulci and gyri are well formed. Dissection of these brains revealed one of the larger branches of the superficial middle cerebral vein lying in each of the three sulci which separate the opercula of the insula. This is what would be expected in view of the fact that the sulci and vessels both radiate from a common point—the stem of the lateral fissure.

The majority of those veins more closely adjacent to the sagittal sinus (i.e. the superior cortical veins) are related to no sulci which correspond with them in direction. The vessels in the posterior portion of the frontal lobe and the anterior portion of the parietal lobe are, however, related to three such depressions—the precentral, central and

postcentral sulci. It is found that each of these sulci contains one of the main superior cortical veins or one of their tributaries. It must be noted that it is only the inferior portions of the vessels which are found in these sulci. It has been stated above that the terminal portion of each vessel has quite a different direction as it enters the sinus. As has been already mentioned, the cortical veins are variable as to their size, and the three vessels now under consideration are no exception. The central vein was, in the series examined, usually large and always a single vessel. The vein in the precentral sulcus, in two cases, had a separate opening into the superior sagittal sinus; but in the remainder of cases it turned posteriorly to enter the central vein. There were usually two vessels in the postcentral sulcus: one in its inferior portion which terminated in the central vein, and another above which either terminated in a similar manner or in a more posteriorly placed vessel. In one case a large single postcentral vein was one of the tributaries of the superior sagittal sinus. In respect of this relationship of veins to sulci, it should finally be pointed out that in all cases a large member of the series was found leaving the surface of the hemisphere in the region of the lateral parieto-occipital fissure en route for the superior sagittal sinus.

For mechanical reasons it would be expected that when a sulcus and an adjacent vein coursed in the same direction, the vein would lie in the sulcus rather than on the summit of a gyrus. Such a relationship would have the advantage of facilitating the circulation by relieving the vein from the pressure of overlying parts.

Lastly, it should be noted that each of the larger of the cortical veins, as it passes from the lateral surface of the cerebrum, receives a large tributary from the medial surface of the hemisphere. The largest of these medial tributaries passed superiorly in the medial parieto-occipital fissure to join the vessel found in the lateral portion of the fissure (which has already been mentioned).

II.—THE CEREBRAL VEINS OF THE ADULT.

In so far as their number and relationship to the cortex are concerned, the vessels of the adult correspond well with those of the foetus. The differences between the veins in the two sets of specimens will now be considered.

(a) *Mode of origin.*—The vessels are usually described as commencing in a capillary zone midway between the lateral fissure and the supero-medial border of the hemisphere. It has been noted in the

description of these vessels in the foetus that at their inferior extremities all the large veins are continuous with tributaries of the superficial middle cerebral vein.

It is considered that in the adult the majority of the vessels have a similar origin. Firstly, it would seem unlikely that any great change in the origin of these vessels would occur after birth. It must be admitted that with the growth of the hemisphere, the venous channel might become attenuated, and only its larger superior and inferior portions remain obvious. In the same way, the growth of the gyri might obscure portions of the vessels which sometimes lie, for a part of their course, hidden in the sulci. Secondly, from observation of fresh post-mortem brains, it is considered that the majority of the larger

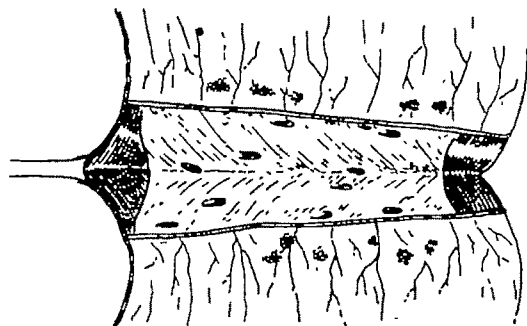


FIG. 4.—Diagram to show platform extending between the walls of the superior sagittal sinus and subdividing its lumen into dorsal and ventral parts. Several arachnoid granulations project into the ventral subdivision.

tributaries of the superficial middle cerebral vein become continuous with the superior cortical veins. It is believed that the description of one anastomotic vein is inaccurate, and that the majority of the large superior tributaries of the superficial middle cerebral vein reach the superior sagittal sinus above. It was noted, however, that the continuity of the more anterior tributaries of the superficial middle cerebral vein (i.e. those on the frontal cortex) with the anterior members of the superior cortical series is lost in the adult. In some cases one or more of the more posterior vessels showed a similar loss of continuity. It is considered that this is due to the further development of the cerebrum, especially in the region of the frontal lobe.

(b) *Mode of termination.*—As in the foetus, the superior cortical veins in all the adult specimens terminated in the superior sagittal sinus. The main facts in the anatomy of this sinus are well known, but in the

course of the dissections certain features which are ignored in the usual descriptions were noted and will now be considered.

The chords of Willis—strands of endothelium passing between the obliquely disposed lateral walls of the sinus—are well known. They are seen particularly in its larger posterior portion. Sargent refers to the folds of endothelium to be seen in relation to the orifices of the superior cerebral veins in the wall of the sinus. These have a valve-like appearance, but can have no such function in that they offer no obstacle to the injection of the cortical veins from the sinus. In several of the

TABLE III.—SHOWING POSTERIOR ANGLES MADE BY THE SUPERIOR CORTICAL VEINS WITH THE SUPERIOR SAGITTAL SINUS IN ADULT SPECIMENS. THE SEQUENCE OF THE ANGLES FROM LEFT TO RIGHT CORRESPONDS TO THAT OF THE VEINS FROM FRONTAL TO OCCIPITAL POLE.

Specimen	Side of hemisphere	Angle between terminal portion of vein and superior sagittal sinus
1	Left	135°; 120°; 50°; — — 20°; — —
	Right	125°; 90°; 50°; 70°; 15°; 10°
2*	Left	90°; 90°; 65°; 65°; 55°; 35°; 25°; 20°; 25°
	Right	90°; 90°; 75°; — 50°; 65°; 65°
3	Left	105°; 60°; 80°; 80°; 50°; 40°; 20°
	Right	100°; 70°; 45°; 40°; 10°
4	Left	120°; 90°; 40°; 45°; 35°; 30°; 30°
	Right	105°; 90°; 55°; 40°; 30°; 20°
5	Left	115°; 90°; 90°; 75°; — 40°
	Right	100°; 80°; 90°; — 80°; 70°; 80°; 80°

* In Specimen 2, there was considerable shrinkage of the frontal lobes.

dissections it was found that instead of these localized folds and bands, a considerable platform existed within the sinus subdividing its lumen into dorsal and ventral portions (fig. 4). These were found in either the anterior or posterior portions of the sinus—sometimes in both—and the largest of them measured 8 cm. antero-posteriorly. Two points of interest were noted in connection with these folds. Firstly, that while on the whole few arachnoid granulations project into the sinus, they appeared to be present in greater numbers beneath the platforms than elsewhere. Secondly, when the orifices of the superior cortical vein are related to one of these platforms the vein always terminates beneath the fold in the inferior subdivision of the sinus.

Lastly, as has been pointed out by Le Gros Clark, it was found that

in every case the veins open into the superior sagittal sinus itself and never into its lacunæ laterales.

(c) *Direction*.—The main points in connection with the direction of the vessels are seen in Table III. It will be seen that the angles are considered in five specimens only. This is due to the fact that in a number of the specimens examined, the small veins in the frontal region had been torn out at their point of entry into the sinus, and no measurement could be made. In other cases, shrinkage of the brain within the skull had so altered the course of the terminal portions of the vessels under consideration that measurement was considered valueless.

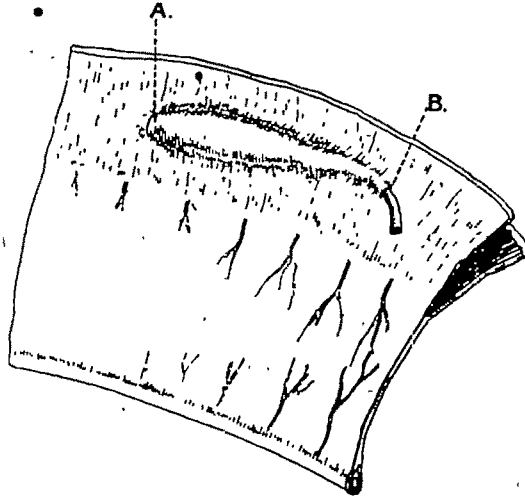


FIG. 5.—Diagram of falx cerebri in an adult. This shows the manner in which a superior cortical vein having reached the lateral wall of the superior sagittal sinus becomes adherent to it and courses anteriorly and slightly inferiorly along it. B, Point at which vein becomes adherent to sinus. A, Point at which vein, having undergone a terminal dilatation, opens into sinus.

When this table is compared with the corresponding one obtained from foetal specimens, the following points are noted. Firstly, the anterior veins in the adult are in most cases found to pass posteriorly into the sinus—in which respect they differ from the corresponding vessels in the foetus, which enter the sinus at right angles to its long axis. At first sight growth would not appear to affect the direction of the more posterior veins. Careful examination reveals, however, that the obliquity of these posterior vessels is greater than the angles would suggest. In the great majority of cases the vein is adherent to the

outer aspect of the sinus, coursing forward upon it for a variable distance before actually terminating in it. This is shown in the diagram (fig. 5). This terminal portion of the vessel is thin-walled and often considerably dilated. It courses not only anteriorly but also slightly inferiorly. The actual length of vein adherent to the sinus wall varies, but may be as much as 8 cm., and would appear to be greater in the most posterior veins. Such adherence of vein to sinus if seen in the foetus affects the most posterior veins only, and to a very slight extent.

Before discussing these points further it might be well to draw attention to irregularities in connection with the course of the terminal portions of the superior cortical veins and to endeavour to explain them. Sometimes, as will be seen from the tables, a posteriorly situated vein will enter the sinus less obliquely than the vein immediately anterior to it—a reversal of the usual arrangement. It is only to be expected that such irregularities would arise, and they may be explained on the assumption that there has been displacement of the venous trunk across the cortex—a displacement which normally does not occur. In favour of this is the fact that such irregular veins are usually small, and not anchored to the cortex by a tributary from the medial surface of the hemisphere. It should also be pointed out again that the apparent obliquity of the posterior veins is less than that actually present since the angle made by a vein with the sinus will depend upon the degree of adherence between the two structures.

DISCUSSION.

In the discussion which follows an endeavour will be made to correlate the above findings with the stages in the development of the cerebral hemispheres.

In this work no attempt has been made to follow the early stages in the development of the veins of the cranial cavity. For the appearances at these stages reference has been made to Streeter's well-known work. It may be useful to summarize briefly the chief points in this connection.

The primary head vein with its three—anterior, middle and posterior—plexuses is well known, the anterior and middle plexuses later fusing to form a single anterior plexus. The vessels in this anterior plexus become separated into three layers: a superficial, which forms the superficial vessels of the head; an intermediate, which forms the dural sinuses; and a deep portion which intimately covers the nervous

tissue and later forms the cerebral veins. Continuity between the superficial and middle venous strata persists only in the emissary veins. The cerebral veins have, however, important connections with the dural system, firstly in the region where both sets of vessels drain into the primary head vein, and secondly, on the dorsal aspect of the cerebrum close to the mid-line. In this latter region there is an anastomosis between the vessels of opposite sides which is called the sagittal plexus, and from this the superior and inferior sagittal sinuses and the straight sinus are developed.

These points will now be considered in relation to the specimens examined for this paper. The insula may be regarded as the nodal point from which the axes of growth of the cerebral hemisphere proceed in various directions. It would be expected that the deepest stratum of the anterior plexus would send some of its anterior branches radiating from this point to the margin of the hemisphere. This arrangement persists in late foetal and adult life, the superficial middle cerebral vein sending its tributaries radiating across the surface of the hemisphere towards its margin. Turning now to the superior cortical veins, as can be seen in the drawings (figs. 1, 2 and 3) and as would be expected on general principles, the inferior portions of these vessels radiate towards the supero-medial margin of the hemisphere in such a direction that if prolonged they would enter the superior sagittal sinus approximately at right angles to its long axis. But the direction of the terminal (superior) portions of the vessels changes, so that in the adult they are directed slightly posteriorly in the case of the one or two anterior veins, and anteriorly in the case of the other veins. This anterior inclination is best marked in the case of the most posterior veins. The obliquity of the terminal portions of the superior cortical veins in the late foetal stages is less well marked than in the adult, and the difference can well be explained by the growth of the cerebrum as will now be seen.

From the observations which have been made above it is considered that in the early foetal stages the superior branches of the superficial middle cerebral vein radiate from the region of the insula and enter the sagittal plexus at right angles to its long axis, there being at this stage no change in the direction of the terminal portions of the vessels.

The region of entry of the vein into the plexus (or sinus) may now be taken as a relatively fixed point. As a result of further growth of the cerebrum certain changes are brought about. Firstly, the radiating tributaries of the primary head vein in the region of the insula would

be elongated and their central portions attenuated. In the case of some of the vessels, a complete separation of the original channel into dorsal (superior cortical vein) and ventral (superficial middle cerebral vein) parts, occurs. Secondly, the growth anteriorly of the frontal pole would lead to a change in the direction of the terminal portions of the superior cerebral veins; while the growth posteriorly of the main mass of the hemisphere would produce a more marked change in the direction of the posterior members of this series of veins. Such a change in direction has been seen in the specimens examined. It was seen that in the foetus the anterior members of the superior cortical group of veins enter the superior sagittal sinus approximately at right angles to its long axis, while in the adult these vessels course backwards to their termination. Similarly, the obliquity of the posterior veins in the superior cortical group has increased in adult life—as is shown by the adherence of the terminal portions of these veins to the sinus wall—a condition which, if found at all in the foetus, is very poorly marked. Only the later stages of this change in direction with growth could be made out in the specimens examined in this instance, but it seems highly probable that the earlier changes are brought about in a similar manner. The examination of the inferior cerebral veins passing from the inferior surface of hemisphere to lateral sinus support this view as to the cause of the direction of the superior cortical veins. These course, for the most part, very obliquely, posteriorly from the cerebrum to the sinus; a course which would be brought about by a forward growth of the temporal lobe—the attachment of vein to sinus being a fixed point. It might also be pointed out at this stage that the inferior anastomotic vein or veins come into existence in the same way as the superior—representing the anastomosis which existed between the most anterior part of the anterior plexus and that portion immediately posterior, which later develops into the transverse sinus.

It may therefore be stated that the direction of any one of the cortical veins depends upon the direction of the growth of the particular part of the cerebrum to which it is related. A study of these vessels will therefore provide an indication as to the axes of growth of the various portions of the hemisphere, and it is possible that an examination of the vessels in lower types might provide information in this direction.

Finally, it is considered that the “chords of Willis”, “valves” and platforms which are to be found in the superior sagittal sinus persist as evidence of its original plexiform character.

III.—THE LACUNÆ LATERALES.

The lacunæ laterales have long been described as lateral projections of the lumen of the superior sagittal sinus between the two layers of the cranial dura mater, and as receiving some or the superior cortical veins of the cerebrum.

Sargent described them in some detail, stating that there are three on each side—frontal, parietal and occipital. He also noted that with advancing years they increase in size. In common with most writers on the subject he stated that the lacunæ receive many of the superior cortical veins.

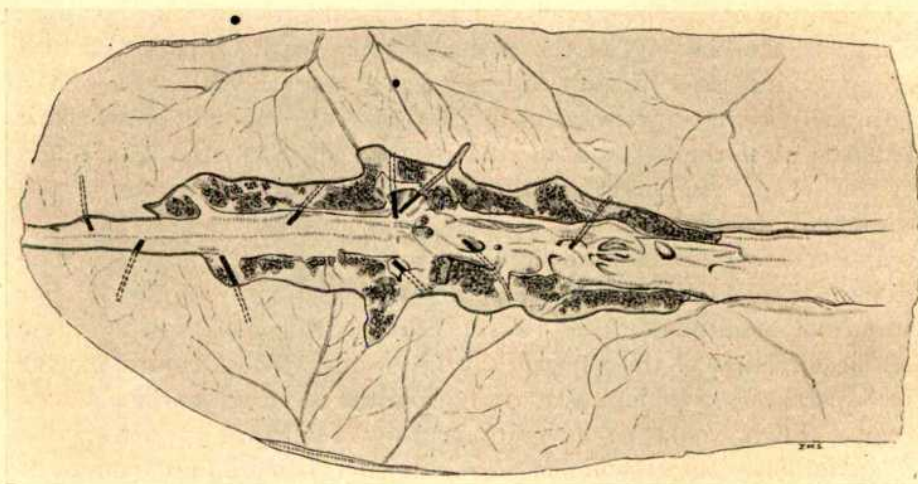


FIG. 6.—Drawing of a dissection of superior sagittal sinus and lacunæ laterales in a subject aged 40. Arachnoid granulations as yet not numerous and lacunæ small but none the less forming a continuous cavity on each side of the sinus. Note extension laterally of granulations into the upper extremity of one of the larger tributaries of the middle meningeal vein on the left side. Bristles have been inserted into the larger superior cortical veins, and the absence of granulations from those portions of the floor of the lacunæ beneath which the veins pass will be noted.

Le Gros Clark pointed out certain important features in connection with these lacunæ which had previously been overlooked. He noted their absence in the foetus, where, occupying the position in which the lacunæ are found in later life, there is a plexus formed by the union of the meningeal and diploic veins. He has produced evidence that the lacunæ develop from this plexus. He noted that lacunæ develop *pari passu* with the arachnoid granulations, and he especially stressed the fact that the superior cortical veins never end in the lacunæ laterales, but always in the superior sagittal sinus itself.

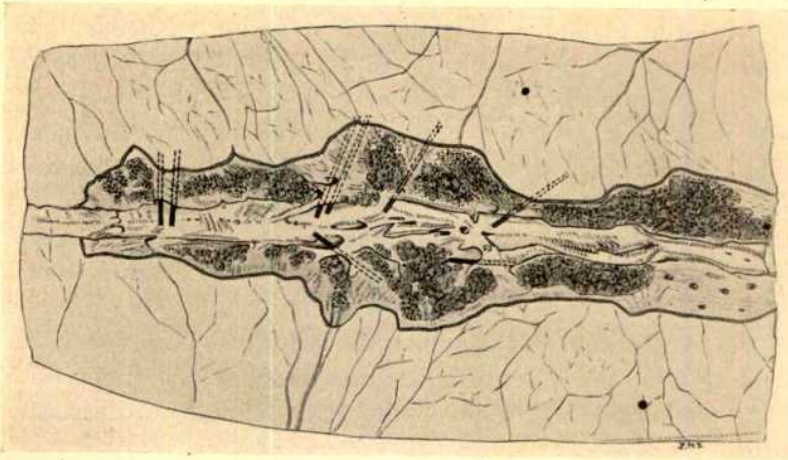


FIG. 7.—Drawing of dissection of superior sagittal sinus and lacunæ laterales in a subject, aged 50. A single lacuna on each side carpeted with arachnoid granulations shown. This carpet is absent only in those regions beneath which a cortical vein passes on its way to the sinus. In spite of careful removal of the specimen the granulations tore away from the posterior part of the left lacuna (remaining attached to the supero-medial margin of the hemisphere—a condition of affairs which is commonly seen).

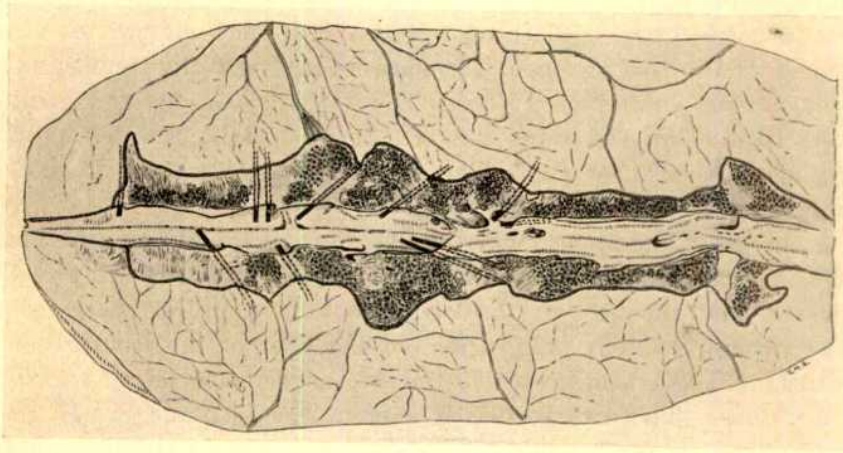


FIG. 8.—Drawing of a dissection of the superior sagittal sinus and lacunæ laterales in a subject aged 55. The confluent lacunæ are again seen and are everywhere carpeted with arachnoid granulations except over the cortical veins as they pass medially beneath the floor. Bristles have again been passed through the larger veins into the sinus to demonstrate this point.

In view of the accepted fact that the lacunæ laterales develop *pari passu* with the arachnoid granulations it seemed possible that they developed as a result of the growth of the granulations (i.e. to increase the venous endothelial surface as demand for such increase arose). An obvious objection to such a hypothesis was the fact that the lacunæ are described as localized outgrowths of the sinus, while the arachnoid granulations have no such localized distribution but form a chain along the supero-medial margin of the hemisphere in its middle portion. Though varying in width in different regions, this chain is continuous in all older brains.

In the foetal specimens, in which the sinus had been distended with coloured gelatin, the absence of lacunæ laterales and the presence of a venous plexus in the region of the lateral angle of the sinus were confirmed.

Dissection of the adult specimens revealed that while in younger subjects the lacunæ laterales may form several separate cavities, in subjects past middle life there is one continuous lacuna on each side of the superior sagittal sinus. This extends from over the posterior portion of the frontal lobe, backwards over the parietal lobe, and sometimes reaches as far as the anterior part of the occipital lobe. It communicates with the sinus by numerous small openings situated in the region of its lateral angle. Its lumen is crossed by numerous fine strands which Le Gros Clark regards as the thinned-out meshes of the plexus found in this region of the foetus. In length the lacunæ in this series measure on average 15 cm. The width is variable and greatest where large meningeal veins run into them. At their widest portion they measure about 3 cm. The drawings of dissections (figs. 6, 7 and 8) illustrate several of these points.

It has been mentioned that relatively few granulations were found projecting into the lumen of the superior sagittal sinus. It is noticeable, however, that the floor of the lacunæ is almost entirely carpeted by these structures. The only regions of the floor of the lacunæ not so covered are those beneath which the cortical veins travel on their way to the sinus. This can be clearly seen in figs. 6, 7 and 8. In these regions there is often some adherence of the roof to the floor of the lacunæ, but these are always very easily separated, much more easily than the two layers of dura mater elsewhere.

One other point was noticed: that while the superior sagittal sinus is itself often full of blood clot, no trace of this is ever found in the lacunæ laterales.

DISCUSSION.

It is well known that the arachnoid granulations are absent at birth. Le Gros Clark states that they are first to be seen at the age of 18 months, and after this the granulations become more numerous and increase in size throughout life. A large proportion—indeed the majority—of these granulations are to be found related to the superior sagittal sinus, and in later life a continuous chain of granulations can be seen along the intermediate part of the supero-medial margin of the hemisphere.

The lacunæ laterales are also absent at birth. It is difficult to state when these first appear, and no reference to the point could be found in the literature. However, having once appeared, the lacunæ increase in size throughout life until, as has been seen, the original series of cavities has been replaced by a single lacuna on each side of the superior sagittal sinus.

Finally, it should again be emphasized that while a few arachnoid granulations are to be found projecting into the venous sinuses themselves, the vast majority lie on the floor of the lacunæ laterales for which they form a thick carpet.

From a consideration of these facts it is believed that the lacunæ laterales not only develop *pari passu* with the arachnoid granulations, but also that their development is due to the enlargement of the granulations, which necessitates an increase in the venous endothelial surface. It is suggested that in early life the microscopical arachnoid villi project into the venous plexus at the lateral angle of the superior sagittal sinus. With the increase in size of these villi to form the granulations the venous plexus also enlarges. The separation between the individual veins in this plexus is gradually lost, and the lacunæ are formed. At first several of these lie on each side of the superior sagittal sinus, but in later life, as a further stage in their development (also dependent on the growth of the granulations) these separate cavities become continuous with one another.

The absence of blood clot in the lacunæ laterales suggests that these contain under normal circumstances little blood, and probably mainly cerebrospinal fluid and projecting granulations. As this fluid passes from the lacunæ into the sinus, the pressure in the former must be higher than in the latter, and thus the flow of blood into the lacunæ is prevented.

To regard the arachnoid granulations as pathological formations, or

what amounts to the same thing, as being the result of increased intracranial tension, would appear to be an error. A progressive growth throughout life appears to be one of the important characteristics of the arachnoid outgrowths, though the functional significance of this continued enlargement is not clear. In this paper all macroscopical arachnoid outgrowths are referred to as granulations.

SUMMARY.

(1) The radiation of the cortical veins from the region of the insula is very well marked in the foetus and persists in adult life. The superior members of this group of vessels approach the margin of the hemisphere at right angles, but their terminal portions, in most cases, change direction before entering the sinus. From observations on the changes in their direction, which occur between the later months of foetal life and adult life, it is considered that all these vessels originally entered the sinus approximately at right angles to its long axis.

(2) With the growth of the cerebral hemisphere, there is a tendency towards the separation of these vessels into (a) a superficial middle cerebral system and (b) a system of veins around the margin of the hemisphere—the superior and inferior cortical veins. In the case of some of the vessels the separation may be complete, but with many the continuity of the original channel is not interrupted, and hence the superior anastomotic veins (at least three in number) and the inferior anastomotic veins (usually two in number) persist as evidence of the original arrangement.

(3) The direction of the cortical veins of the cerebrum is determined by the growth of the cerebral hemisphere. As a result of the growth anteriorly of the frontal lobe and posteriorly of the main mass of the hemisphere, the direction of the terminal portions of the superior vessels is altered, the anterior veins being directed posteriorly and the posterior veins coursing obliquely anteriorly as they pass to the superior sagittal sinus. The posterior inclination of the inferior veins, as they pass to the transverse sinus, has a similar explanation.

(4) One of the members of the superior cortical series of veins is found in each of the precentral, central and postcentral sulci, and similarly a tributary of the superficial middle cerebral vein is found in each of the sulci which separate the opercula of the insula.

(5) The statement that at birth the lacunæ laterales are absent, and later appear and grow *pari passu* with the arachnoid granulation has been confirmed. Further, it has been found that in subjects past

middle age the lacunæ laterales are two in number—one being placed on each side of the superior sagittal sinus.

(6) The lacunæ laterales serve as lateral extensions of the lumen of the superior sagittal sinus over the supero-medial margin of the cerebral hemisphere in the posterior frontal, parietal and sometimes also the anterior occipital regions, where the majority of the arachnoid granulations are found. The floor of each lacuna is everywhere carpeted by a layer of these granulations.

In conclusion I should like to express my indebtedness to Professor Woollard for suggesting this piece of work to me, and for his unfailing interest and much helpful advice while it has been in progress. And also to Miss Z. M. Stead for the very great care which she has bestowed upon the drawings.

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HEMICHOREA ASSOCIATED WITH A LESION OF THE CORPUS LUYSII.

BY JAMES PURDON MARTIN AND N. S. ALCOCK.

IN 1927, one of us (J. P. M.) [12], described a case in which hemichorea of unusual violence and sudden in its onset was associated with a small hæmorrhage which had destroyed the corpus Luysii on the opposite side of the brain. The first object of the present paper is to describe another similar case.

The patient, F. W., was a man aged 65, a manufacturer's agent, who was admitted to the National Hospital, Queen Square, under the care of Dr. C. P. Symonds on November 4, 1933. He had had no illness until the symptoms about to be described, but examination at the time of his admission to hospital showed that his arteries were very sclerotic, his blood-pressure 210 mm. Hg systolic and 130 mm. Hg diastolic, and a number of small hæmorrhages had occurred in the fundus of the left eye. His heart was enlarged in association with the raised blood-pressure and the second cardiac sound was accentuated; there were no murmurs and the cardiac rhythm was normal.

Seven days before his admission to hospital the patient was sitting in a café with his wife and suddenly his left foot began to work about in an irregular fashion. The movements ceased after a few minutes, but later in the day the left arm and the left leg suddenly began to make large irregular movements and these persisted and quickly became very violent. The patient spent a restless night and because of his wild movements he could not keep the bed-clothes over him. He was seen by his doctor on the second day. He was then able to talk and gave an intelligent history. Violent jerking movements of the left arm and leg were going on, his arm being thrown at times against the arm of his chair and his foot struck the fender. He could exert some voluntary control over these movements, and the doctor noticed that he could take his glasses off and put them on "by happy shots." The patient said he had no headache. He was able to walk and walked a distance of about 500 yards to the doctor's house. On the fourth day he began to have delusions and complained of people who, he imagined, were in his room. He referred to events of thirty years ago as if they had recently happened. On the fifth day he was admitted to hospital and spent a bad night, writhing and frequently shouting. On the sixth day he was rational at times but deluded for considerable periods. On the seventh day his movements were very violent and his breathing began to be rapid. He was rational at times and he recognized his

wife. He was admitted to the National Hospital, Queen Square, on the eighth day, but he died within a few hours of his arrival.

At the time of his admission the patient's temperature was normal; his pulse-rate varied within a short period from 90-120; the respiratory rate was 40-50 for the few hours that he was in the hospital before he died.

The most striking feature of his condition was wild choreic movements of the left arm and left leg. The movements were irregular and involuntary. They usually involved the whole limb and were of large amplitude. The left arm might be momentarily still and then flung off the bed in a wild manner and the left leg might be suddenly flexed or lifted from the bed or rotated. Consecutive movements showed no resemblance to each other. The movements of the arm and leg seemed independent as regards time, the leg possibly being still for a few seconds while the arm was being flung about. Both the affected limbs showed numerous bruises. The movements could be controlled by voluntary effort for a few seconds and for that length of time the patient could lie still.

He talked with difficulty and was at times almost inarticulate. He was normally orientated; he knew he had come to hospital; his memory seemed fairly good and, although he was writhing about in bed, he was moderately alert and attentive and co-operated in the examination, so that even vibration and postural sense could be tested. Detailed examination of the nervous system did not reveal many abnormalities apart from the involuntary movements already referred to. The optic discs were normal but hæmorrhages were present in the left retina; the pupils were rather small and were not quite equal, the left being the larger; they reacted to light but not very briskly. An old convergent strabismus of the left eye was present, but otherwise the ocular movements were normal. Movements of the face were symmetrical and no abnormal movements were noticed in the face. Movements of the jaw, palate and tongue were all normal. In the limbs no weakness was discovered. Tone appeared to be diminished in the left arm, the left hand could be thrown so as to hit the face but no such phenomenon was present on the right side; there was no definite diminution of tone in the left lower limb. Co-ordinated movements could be carried out and the patient was able to touch his nose with his forefinger, although during the action his finger might suddenly be thrown by the violent movements of his arm a foot or so from its goal. Similarly heel-knee tests and toe-finger tests could be carried out, though with wild choreic ataxia. Pin prick was normally appreciated on all the limbs, and touch and vibration were recognized. All the tendon-jerks were present and normal and both plantar reflexes were flexor.

The diagnosis postulated by Dr. Symonds was a small hæmorrhage destroying the corpus Luysii on the right side. Death occurred from cardiac failure on the eighth day from the onset of the symptoms.

A *post-mortem* examination was performed by Dr. Greenfield forty-eight hours later. It was noticed that the left arm and leg were covered with bruises and scratches, and in places were quite denuded of skin. The heart

was very dilated. The aorta was extremely atheromatous and showed some general dilatation. In the lungs there were some old fibro-caseous tuberculous lesions at the apices; there was no pneumonia. Nothing abnormal was observed in the liver, spleen, stomach, intestines or kidneys. The brain showed no external evidence of softening or hæmorrhage. The arteries at its base were very atheromatous, and there was an old fibrous clot in the left internal carotid artery just below the point where it branched at the formation of the circle of Willis.

After the brain had been allowed to harden in 10 per cent. formol-saline

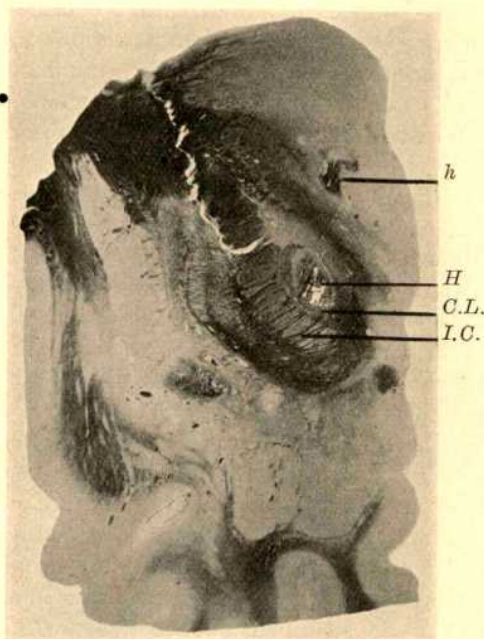


FIG. 1.—A horizontal section through the upper part of the lesion X 1·7. *H.* hæmorrhage in the corpus Luysii; *h.* minute hæmorrhage in the thalamus; *C.L.* corpus Luysii; *I.C.* internal capsule.

horizontal sections were made through the cerebral hemispheres and brain-stem at 5 mm. intervals. A small recent hæmorrhage, about the size of a pea, was found occupying the greater part of the right corpus Luysii; part of the anterior and lateral portion of the nucleus was spared and the lesion did not touch the internal capsule. There was also a minute hæmorrhage at a slightly higher level in the right thalamus about $\frac{1}{2}$ cm. anterior to the posterior commissure. Careful examination of the rest of the brain did not disclose any other lesions.

In order that the extent of the lesions might be examined in detail, blocks were prepared including the whole of the thalamus, sub-thalamic region and

basal ganglia. Those which included the hæmorrhages were cut in serial sections. Examination of these showed that the larger hæmorrhage occupied the site of the greater part of the right corpus Luysii. It extended medially beyond the margin of this ganglion and involved the zona incerta and interrupted Forel's bundle H.2; it did not reach H.1 nor affect the ansa lenticularis. When the sections were examined in series from above downwards, no hæmorrhage was seen in a section through the highest part of the capsule of the corpus Luysii, but it appeared in the next section, occupying a small area in the medial half. In the succeeding sections it rapidly attained its full size (figs. 1, 2 and 3). It was oval in horizontal section measuring

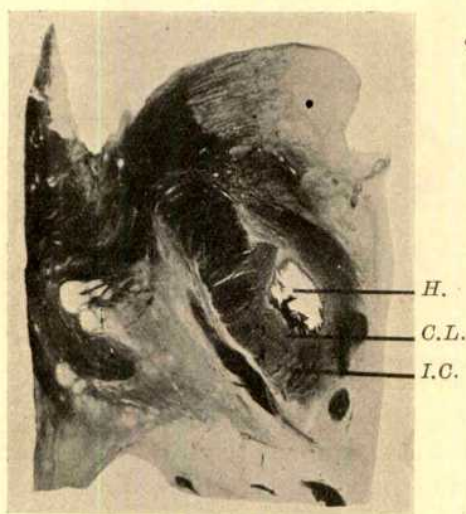


FIG. 2.—A horizontal section through the widest part of the lesion X 1·7. A margin of the corpus Luysii remains between the lesion and the internal capsule. *H.* hæmorrhage in the corpus Luysii; *C.L.* corpus Luysii; *I.C.* internal capsule.

about 8 mm. by 4·5 mm. at its widest part. It occupied the medial three-quarters or so of the corpus, leaving between the border of the lesion and the internal capsule a margin which, at its narrowest part, was about 1·5 mm. (fig. 2).

In the inferior half of the corpus Luysii the hæmorrhage showed a gradual decrease in size from above downwards, and in many of the lower sections a large fraction—amounting probably to about half—of the exposed area of the ganglion, remained intact. The hæmorrhage was less oblique in direction than the corpus Luysii, and consequently the lower part of the lesion occupied a more posterior position in the ganglion than the upper, and the largest intact mass of corpus Luysii was towards its anterior (inferior) pole (fig. 3).

The hæmorrhage ended immediately below Luys' body, its lower limit

being situated mid-way between the substantia nigra and the red nucleus. The lesion did not occupy any part of the substantia nigra.

The hæmorrhage in the right thalamus was much smaller in all dimensions and was seen in only a few sections (fig. 1).

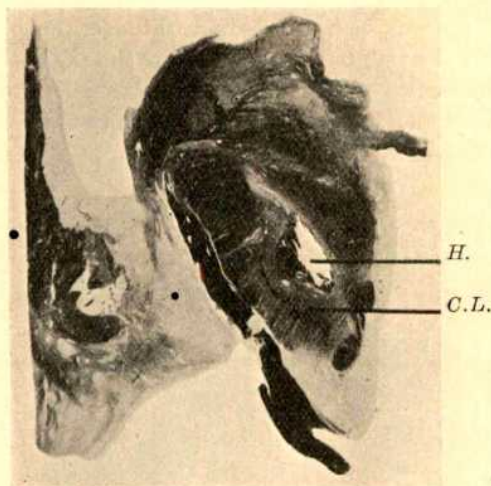


FIG. 3.—A horizontal section through the lower part of the lesion X 1.7. The largest remaining portion of the corpus Luysii is towards its anterior pole. *H.* hæmorrhage in the corpus Luysii; *C.L.* corpus Luysii.

This case reproduces many of the features of Martin's [12] case to which we have referred and to others which have been recorded. Clinically it showed the same violence and large amplitude of the involuntary movements—that severity of hemichorea to which Economo gave the name "Hemiballismus." An unusual point which will be referred to later is the absence of choreiform movement in the face. Pathologically, the lesion found was smaller than in Martin's case, and a larger fraction of the corpus Luysii was spared on its lateral side; its medial extent was much the same as in the former case. In the present instance there was also a minute lesion in the thalamus, but it does not seem that any clinical importance can be attached to this.

The case adds to the rapidly increasing body of evidence that a subthalamic lesion damaging the corpus Luysii results in, and has as its clinical counterpart a violent hemichorea (hemiballismus) of the opposite side of the body. Martin's search of the literature up to 1927 revealed a number of cases of violent hemichorea in which the only cerebral

lesion found was a small subthalamic one similar in site and size to that in our case. Such were the cases of Fischer [8], Campora [5], Pette [16], Canfield and Putnam [6], Economo [7], Jakob [10]. Since then cases practically identical with these in their clinical and pathological features have been described by Matzdorff [14], Spatz [20], Schaffer [19], Chr. Jakob [11], v. Santha (1928) [17], Pelnar and Sikl [15], Uiberall u. Samet-Ambrus [22], v. Santha (1932) [18]. There can consequently be little doubt that a lesion in this site has "hemiballismus" as its result.

Of less value than these cases are others in which there have been found either somewhat larger lesions involving the same structure, or multiple lesions, one of which lay in the site referred to. Such among older cases are those of Greiff [9], Touche [21], Bianchi [2], and Bremme [4], and in the more recent literature those of Balthasar [1], Bonhoeffer (1930) 2 cases [3], and Wulff [23].

The lesions destroying the corpus Luysii in these cases have been of the most diverse nature. In many instances they were hæmorrhages, in others softenings, in several cases small secondary carcinomata, in those of Bianchi [2], Bonhoeffer [3] and Wulff [23] tuberculomata.

The symptoms in many cases have existed for only a few weeks before death, but in other instances they have been present for months—nine months in that of Touche [21], nineteen months in v. Santha's first case [17], five and a half months in his second [18]. Many of the patients have been elderly or at least middle-aged, but Bianchi's [2] first patient was a lad, aged 18, and Bonhoeffer's [3] second (1930) a child, aged 7.

In nearly all cases the symptoms have involved the whole of one-half of the body, but in our present case they completely spared the face. Von Santha [18] too, described a case (his second) in which the head and face and muscles of articulation were unaffected. In that instance considerable improvement in the patient's whole condition occurred during the first six weeks and the patient lived five and a half months. It was found, post-mortem, that the lesion—a hæmorrhage—involved the corpus Luysii chiefly dorsally and medially and that the anterior (oral) pole was spared. Comparing his two cases v. Santha argued that there was a "somato-topical" relationship between lesions of certain portions of the corpus and chorea of parts of the body—the antero-medial or oral pole being associated with the face, the middle part with the upper limb and the posterior portion with the lower limb. From what we know of the function of other structures in the brain it is likely *a priori* that some

such "somato-topical" correspondence exists in the corpus Luysii. In our own case the largest intact portion of the corpus was towards its antero-medial (oral) pole and it seems legitimate to associate the sparing of this portion with the absence of choreic movement in the face. Our findings are thus consistent with, and to that extent support, v. Santha's suggestion.

It is important that we should bear in mind that there are in the literature a few cases of symptomatic hemichorea with adequate and reliable pathological descriptions in which the lesions found did not primarily involve Luys's body. In the present state of our knowledge these records assume a special importance, and in association with cases such as that which we have described they raise certain definite questions, the more important of which may be briefly discussed here:—

(1) In instances as such ours, with small subthalamic lesions, is the corpus Luysii the actual critical structure, damage of which has hemichorea as its result?

(2) May hemichorea result from lesions elsewhere, i.e. from damage to structures other than the corpus Luysii (and its emergent fibres)?

(3) If so, does the chorea resulting from a lesion of the corpus Luysii differ from that which results from lesions of other structures, and does it differ from other choreas?

(1) As cases such as that which we have described accumulate it seems more and more likely that the first question is to be answered in the affirmative.

Since attention was directed to the importance of the subthalamic lesion, no case of "hemiballismus" has been fully described in which the corpus Luysii has not been damaged. A partial exception to this statement is provided by a case of Nikitin's, mentioned by von Santha, but no first-hand account of this case seems to have been published. The very restricted subthalamic lesion in our own case involved, in addition to the corpus Luysii, the structures immediately adjoining it on its medial side, viz., Forl's bundle H.2 and the zona incerta. These latter have admittedly been affected in the majority of cases recorded, but Matzdorff's [14] case, in which the damage was entirely within the corpus Luysii, provides one instance in which they were certainly intact, and there are others such as Fischer's [8], in which they were probably undamaged. In the case of Wenderowicz [36],

about to be described, the lesion was on the lateral side of the corpus and remote from these medial structures. No essential significance for the occurrence of the hemichorea can, therefore, be attached to overflow of the lesion beyond the medial margin of the corpus Luysii, and injury to the corpus itself seems to be the only damage that is common to the various cases recorded.

The case described by Wenderowic [36] requires special mention, for our interpretation of it is different from that which Wenderowic himself adopted. An irregular hæmorrhage extended as a narrow band across the internal capsule and reached the corpus Luysii; it had then spread antero-posteriorly along the lateral margin of the corpus Luysii but invaded the nucleus only a little. Wenderowic estimated that not more than one-tenth of Luys's body was actually destroyed, and, finding it relatively intact, he attributed the chorea to "irritation" of the internal capsule. The clinical course of this case was unusual. The patient had suffered at the beginning from hemichorea of extreme violence; but in the succeeding ten days the movements had lost their characteristic fierceness and eventually had almost entirely subsided. Now it is to be expected that the corpus Luysii, lying in the margin of the lesion and involved in it, would at first be put completely out of action and would later in great measure recover its function. Allowing for such recovery we may associate the chorea with the disturbance of Luys's body and it is apparent that such a view not only brings the case into conformity with others but it offers an adequate explanation of the course of the symptoms. The lesion in this case was so placed that there seemed to be no structures other than the internal capsule and the corpus Luysii (and its fibres) to disturbance of which the symptoms could be ascribed.

(2) Does chorea occur as a result of local lesions elsewhere than in the corpus Luysii (or its emerging fibres) ?

One of us (J.P.M.), writing in 1928 [13], expressed the view that there was no valid evidence that focal injuries above the body of Luys resulted in chorea. We began to write this present section in the belief that this view would have to be modified, as it seemed that there were certain recently recorded cases which, taken in conjunction with a few of the older ones, provided sound argument to the contrary. Critical examination, however, shows that valid evidence in this regard is lamentably scant.

Wilson [38] described a case, the importance of which for our present argument is that it showed that the corpus Luysii might be

found apparently normal in a patient in whom violent hemichorea had come on suddenly. In this instance the involuntary movements were of eleven years' duration and the patient was aged 88 years; no vascular lesion was found to which the symptoms could be ascribed, and Wilson attributed them to atrophy of the post-central gyrus. The changes found being degenerative in nature, this case does not strictly belong to the group we are discussing, but its theoretical importance is apparent.

A case which might be important if published in full is that of Nikitin, already mentioned. The lesion was a fairly large one in the thalamus and "the ventral border of the lesion coinciding with the ventral boundary of the thalamus, approaches in many sections to within 2 mm. of the dorsal surface of the corpus subthalamicum (Luysii) which is left intact." Only a brief précis of this case is available.

Very similar to this is an earlier case described by Lewandowsky and Stadelman [30]. The lesion was a large one involving the lateral part of the thalamus and the internal capsule; it extended down into Forel's field. The corpus Luysii is not mentioned, but the pathological description of the case is fairly full, and if this nucleus had been damaged that fact would probably have been observed and referred to.

It may be that a lesion of the thalamus can give rise to hemichorea, but we do not consider that either of these cases is decisive. In both instances the lesions came so close to the corpus Luysii that fibres emerging from it may have been interrupted, or the function of the ganglion itself may have been impaired by circulatory disturbances or otherwise. For this reason the cases do not provide positive evidence that damage to another structure results in the appearance of chorea.

There are also two cases of hemichorea with thalamic lesions described by Zannoni [39] and by Malan and Civalleri [32]. In each instance the damage was in the upper part of the ganglion. In neither case is any illustration given: Zannoni's account is quite inadequate and the other is too confused to have any value as argument. These writers were not aware of the importance of the corpus Luysii in relation to hemichorea.

When we review the cases which showed lesions of the corpus striatum we do not find much more solid foundation for any conclusion. The older cases of Vogt [34], of Conos [26], and of Austregesilo and Gallotti [24] are worthless because of the inadequacy of the pathological examinations and insufficient attention to subsidiary lesions. Weil [35], who has contributed the most recent case of this group, found

changes, apparently of a primary nature, in the corpus Luyyii, so that his case cannot be used to discriminate. The same applies to the case of Lloyd and Winkelman [31], for in it a hæmorrhage extended across the internal capsule and "impinged upon the corpus Luyyii."

The only good evidence is supplied by the case described in 1926 by Fragnito and Scarpini [28]. In that instance the brain was thoroughly and carefully examined. The corpus Luyyii was not specifically mentioned in the description, but Professor Fragnito subsequently informed one of us (J.P.M.) by letter that he had re-examined the sections and that the corpus Luyyii, champ de Forel and medial lemniscus were absolutely intact. The patient was an old man of 80. Hemichorea of the left side had come on suddenly in association with an epileptiform seizure, three years before death, and had persisted. It affected the upper limb more than the lower. The only lesion found in the right side of the cerebrum was a softening in the right corpus striatum. It lay chiefly in the medial portion of the putamen, extending both backwards along the external medullary lamina, and forwards, close under the anterior border of the internal capsule, to affect slightly the head of the caudate.

For the purpose of our present inquiry this is the only important case of its kind in the literature.

In association with such cases it will be recalled that experimental lesions of the corpus striatum have entirely failed to produce chorea. The experiments of Kinnier Wilson [37] on the lenticular nucleus and the later series by Delmas-Marsalet [27] on the caudate may be mentioned; in no instance did chorea or any symptom comparable to chorea result from a lesion of these structures.

As regards chorea attributable to focal lesions entirely below the corpus Luyyii it is perhaps sufficient to state that no such case has been recorded since 1894—a period of thirty-seven years, and the most active thirty-seven years in the whole history of neurology. In 1894, Bonhoeffer [25] described his famous case on which the "Bindearm" or cerebello-cerebral theory of chorea was founded, and it is well to remember that even in that case more than one lesion was present.

The answer to the question whether *focal* lesions of structures other than the corpus Luyyii and its emergent fibres may result in chorea must simply be "not proven." Though in a few instances the corpus Luyyii has been found intact, over a period of many years only one case has been described, which seems to provide sound evidence that a focal lesion of another structure may give rise to chorea. The impression

left on one's mind is that the very scarcity of such cases renders even this evidence suspect.

(3) Is the chorea associated with destruction of the corpus Luysii in any essential way different from other choreas?

All observers who have described cases of hemichorea (hemiballismus) associated with destruction of the corpus Luysii have been struck by the extreme violence of the involuntary movements and their large amplitude. The latter character is due to an unusual degree of involvement of the proximal portions of the limbs. It is doubtful, however, whether either of these features denotes any essential difference from the involuntary movements that are seen, for instance, in Huntington's chorea.

The movements of chorea, as far as we can determine from clinical observations and from the analysis of cinematographic films, are completely irregular and they are *free* movements, not associated with any increase in the tone of the muscles of the affected limbs, and usually with some apparent decrease of it. As such movements increase in intensity there may be an appearance of change in their form. With a mild chorea a weak contraction occurring in the deltoid is not sufficient to raise the weight of the limb and consequently, although such contractions are occurring, abduction of the whole limb is not a pronounced feature of the involuntary movements, and, in fact, may be scarcely observable. But when the chorea becomes more violent the contractions which occur in the deltoid are of sufficient force to elevate the whole arm and consequently abduction becomes a pronounced and very striking feature. Similar considerations apply to movements of the trunk. Herz [29] made cinematographic studies of "hemiballismus" and of other forms of chorea, e.g. Huntington's and senile chorea, and he was unable by analysis of his films to find any difference other than in the violence of the movements, i.e. a difference of degree and not of quality. We have seen movements of abduction of the whole arm—movements characterized by their large amplitude—in a case of Huntington's hereditary chorea. Because of these various considerations we do not see any essential difference, but only one of degree, between the hemichorea in cases such as we have described and chorea resulting from other causes.

There may be some advantage in employing the special term "hemiballismus" for such an unusual and remarkable symptom, but if it is employed it should, in our opinion, be used to denote a special intensity of hemichorea and not a special form of it.

CONCLUSION.

In describing and discussing this case we have not lost sight of the wider issues which the subject raises. However interesting or instructive the study of the underlying lesions of chorea may be, it is well that we should recognize the limitations of this method of approach. Such material does not help us directly to discover where or how choreic impulses arise. If, however, we could determine that damage to certain structures, without gross involvement of any others, uniformly gave rise to chorea, we would then be in a position to investigate the subject from the other side and endeavour to determine what structures must be intact in order that chorea may occur. Along this road seems to lie the approach to the more fundamental problems of chorea. Where do the impulses arise? By what paths do they travel? In what functional system do they exist? How do they exert their influence on movement? And, finally, how are they controlled by the corpus Luyssii?

SUMMARY.

A case is described in which violent hemichorea of the left side came on suddenly in an elderly man: post mortem it was found that a small hæmorrhage had destroyed the major portion of the right corpus Luyssii, there was also a minute lesion in the posterior part of the right thalamus.

As cases of this kind accumulate it becomes more and more likely that the corpus Luyssii is the critical structure, damage to which results in hemichorea.

Reliable evidence that focal damage to any other structure in the brain results in hemichorea is extremely scanty.

"Hemiballismus" consequent on a lesion of the corpus Luyssii does not, in our opinion, differ from other choreas except in intensity.

It is a pleasure to express our gratitude to Dr. Symonds for the gift of the pathological material of this case, to Dr. Greenfield for help in its investigation and to Dr. Meadows for clinical notes.

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THE DISTURBANCES AFTER LAMINAR THERMO-COAGULATION OF THE MOTOR CEREBRAL CORTEX.¹

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THE complexity, both structural and functional, of the cerebral cortex is indeed perplexing. The architectonical studies of Hammarberg, Campbell, Brodmann, Vogt and others, in revealing a subdivision of the cortex in a number of layers of nerve-cell bodies, are apt to make one overlook the fact that the histological investigations of Golgi, Cajal, Kölliker and others who came after them, have demonstrated that these layers are most intricately interwoven. The processes of the constituent nerve-cells of each layer—with the exception of the first, the most superficial one—ramify extensively into many of the other layers, often into as many as four or five of them. Thus one finds, on the one hand, indications of separation and differentiation in functional activity and, on the other hand, structural evidence of close correlation and interaction between the various cortical layers.

If we are to progress in unravelling the intricate functions of the several layers at this level of the central nervous system, one of the most obvious ways is artificial simplification of its structure. To accomplish this the method of laminar thermocoagulation was devised. This method allows us to destroy at will any number of consecutive layers of the cortex (starting from the surface), and to leave the other (inner) layers intact. The principle of the method is very simple. Local application of moderate heat to the exposed cortex for short periods of time results in destruction of the nervous tissue; by using different temperatures and different periods of application it is possible to "dose" the depth of the destruction, and thus to produce laminar lesions. Application of the "coagulator" or "thermode" heated at 65° C. for two seconds destroys the nerve-cells of the outer two layers; 70° C. for three or four seconds results in death of the outer three or four layers. If the thermode, heated at 80° C., is applied for five seconds all the nerve-cells throughout the whole thickness of the cortex are killed.

¹ Preliminary Report in *Naturwissenschaften*, 1934, No. 1, p. 10.

The histological preparations of the lesions produced by this method of laminar thermocoagulation show invariably remarkably sharp boundaries of the lesions. In the acute preparation (survival period up to two weeks) they reveal themselves as circumscribed areas of devastation, in which after a survival period of less than forty-eight hours all nerve-cells have disappeared, sharply delimited from the surrounding normal cortical tissue. The continuity of the surface of the cortex is unbroken.

For a full description of the method and the lesions the reader is referred to previous papers [1 to 6].

In two of these papers [3, 5] it was shown that apparently normal motor reactions can be obtained from the motor cortex on electrical stimulation after destruction of its outer three layers.¹ In such a cortex the only layers present intact are the inner two layers, the layer of the large and giant pyramidal cells and that of the multi-form cells. The excitability is often found to be perfectly normal, i.e. the threshold for monopolar faradic stimulation after the destruction of the outer three layers is the same as before the laminar thermocoagulation. Furthermore, evidence was produced indicating that the reactions from the motor cortex are in all probability elicited by the direct electrical excitation of the bodies of the large and giant pyramidal cells of the fourth layer, and that in the normal cortex, when the outer three layers are also present, "neither the direct electrical excitation of the dendritic processes of these cells ramifying in the upper cortical layers, nor the excitation of the nerve-cells of these superficial layers is essential in the elaboration of the stimulatory cortical reactions. At least no experimental evidence was met which favoured the view that the superficial layers play a rôle."

Faradic stimulation of the cortex is a very useful method of investigation, but one should always realize that fundamentally it is a rather crude means of functional exploration of such a highly complex structure as the cerebral cortex is. For this reason, and in regard to the experimental results mentioned above, it became of interest to compare in the monkey the disturbances following thermocoagulation of the whole thickness of the cortex of the motor arm area (80° C. for five seconds) with the clinical picture following destruction by thermocoagulation of

¹ The scheme of the structure of the cerebral cortex adopted here is that of Brodmann, although the writer is fully aware of the various criticisms which have been brought against it. The main reason for adhering to this scheme is a practical one, the consideration that it is the fundamental and still most widely known conception of the structure of this level of the nervous system.

the outer three layers of the cortex over the same area (70° C. for three seconds).

Fig. 1 represents diagrammatically the right hemisphere of the brain of a monkey (*Macacus*), in which the exposed portion of the precentral arm area, which was thermocoagulated in these two series of experiments, is indicated.

Series I.—Thermocoagulation of the whole thickness of the cortex of the precentral arm area. The clinical picture in these monkeys is essentially the same as after surgical extirpation of this area: a total paralysis of the contralateral arm for a number of days, which gradually

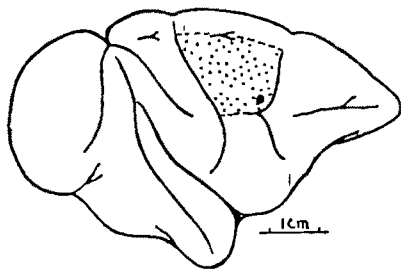


FIG. 1.—Precentral arm area on surface of right hemisphere in monkey (*Macacus*).

subsides until after three or four weeks motor disturbances, are no longer detectable.

The following protocol is illustrative:—

*Monkey. Macacus rhesus.*¹

February 28, 1933.

- 14.15 Ether anaesthesia. Sterile exposure of a large portion of the surface of the right hemisphere with skin, bone and dural flaps. Thermocoagulation of the whole precentral arm area, so far as it lies on the surface of the brain, at 80° C. for five seconds. This is done by multiple contiguous applications of the thermocoagulator, heated at 80° C., each time for five seconds. The cortex over the heated area has a totally bleached appearance.

The wound is closed in the usual way, in the regular separate stages.

- 15.30 Animal back in cage.

- 15.45 Monkey hopping around. Left arm extended and without any motion. Animal can stand on both legs, although occasionally he tends to tip over to the left side, but immediately checks such falling movements.

¹ All data irrelevant to the problem at hand, such as electrical stimulations, &c., are omitted from this and the following protocol.

- 24.00 Animal entirely recovered from narcosis. Walking around. No longer any tendency to fall over to the left side. Uses *left* hand and arm in walking. Does not use hand in defence, to pick up food or to scratch. The left arm is held less extended than this afternoon. Occasionally, when the animal sits quietly, the left hand is put down in abnormal positions, e.g. with the fingers flexed so that the dorsum of the last two phalanges touches the floor of the cage; usually, however, the hand is put down quite normally, resting on its palm. During walking the left hand is always put down normally, at least as long as the observation is continued, i.e. for over half an hour.

March 1.

- 9.00 Distinct improvement of motility of the left arm and hand. Although the animal uses it less than the right upper extremity, he often picks up a grape with the left hand, or takes hold of a stick which is pushed into the cage. The monkey also uses the left hand to push food out of his left mouth pouch into the mouth. The left arm is readily bent now in various movements.

March 2.

- 9.00 Animal uses his left arm much less than yesterday. He has only once been seen to use this arm to grasp a stick which was pushed into the cage; the animal does not pick up food with it. Uses left arm normally in walking; does not put it down in abnormal positions.

- 22.00 Same picture as this morning.

March 3.

- 9.10 There is a little improvement to-day, in so far as the animal occasionally uses the left hand in grasping a fruit.

March 4.

- 9.15 Animal uses his left arm and hand better than yesterday. Picks up grapes with it. Uses it quite well in climbing; hangs from ceiling of cage with both feet and left arm. Once he hangs on left arm only before jumping down to the bottom of cage. Monkey uses left arm definitely less than right one. Empties his left pouch with left hand, by pushing dorsum of hand in normal way against cheek. Movements of left arm in walking are normal.

March 7.

- 14.30 Wound healed by primary intention. Re-exposure of the right hemisphere. The thermocoagulated area is sharply defined by a slight yellowish discolouring of the cortex. Along the sulcus centralis a very narrow strip of cortex, less than $\frac{1}{2}$ mm. wide, is normal in appearance. From a few points in this strip of cortex some movements of the thumb, fingers and wrist can still be elicited on monopolar stimulation at 7 cm. coil distance (very strong stimulus). Immediately inside the heated area, only $\frac{1}{2}$ mm. away from the

excitable points inside the narrow strip of cortex along the sulcus centralis, the cortex is found to be silent, even at 5 cm. coil distance.

Animal killed by ether. Brain in 95 per cent. alcohol for subsequent histological examination.

In other similar experiments, the stage of paralysis of the arm contralateral to the thermocoagulation lasted for six to nine days; then gradual rapid recovery became evident, so that in three or four weeks motor disturbances were no longer detectable.

Series II.—In this series the cortex on the surface of the precentral arm area was thermocoagulated, but only at 70° C. for three seconds, which destroys only the outer three layers. The following protocol may serve as an illustration:—

Monkey. Macacus rhesus.

April 7, 1933.

- 14.10 Ether anæsthesia. Exposure of a large portion of the surface of the right hemisphere under sterile conditions in the usual way.
- 14.25 Cortex of the whole precentral arm area on the surface of the hemisphere is thermocoagulated by multiple, contiguous applications of thermode at 70° C. for three seconds. This destroys the outer three layers of this area. Closure of the wound in three stages. Operation finished at 15.55.
- 17.00 Animal hopping around in cage. Alert. Uses left hand as much as right one. There is perhaps a slight clumsiness in the finer movements of the fingers, as in skinning a banana or picking fleas. In all other movements, not only of shoulder and elbow, but also of the fingers, disturbances cannot be detected.
- 20.00 No motor disturbances are observable. Even the finest movements are executed with apparently normal precision:

April 8.

- 9.00 Animal in excellent condition. Alert. Aggressive. No disturbances detectable in left arm.

April 14. Wound healed primarily. Animal in excellent condition. No disturbances have ever been observed after the first day.

- 11.00 Animal killed with ether. Brain in 95 per cent. alcohol for future histological examination.

In this experiment very mild motor disturbances, i.e. a very slight clumsiness in the finer movements of the contralateral hand, were observable for a few hours. Three hours after the laminar thermocoagulation these very slight symptoms of motor deficit were still noticeable. Six hours after the destruction of the outer three layers these symptoms had disappeared and no trace of any disturbance could

be detected. In another monkey no symptoms could be noticed even two or three hours after the laminar thermocoagulation, in others the slight symptoms of motor deficit lasted a little longer. The longest period through which such scanty, rapidly decreasing symptoms of impairment in the execution of finer movements of the contralateral hand could be detected has until now been seventeen hours.

DISCUSSION.

The results of these two series of experiments are clear cut. In the first series, in which the whole thickness of the precentral cortex of the arm area on the surface of the hemisphere was thermocoagulated, typical severe symptoms of motor deficit appeared. Initially a total paralysis of the whole arm was apparent, gradually subsiding through

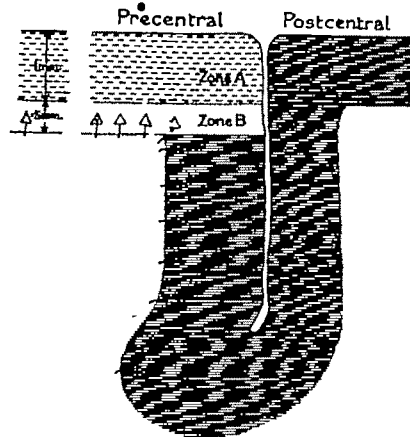


FIG. 2.—Diagram showing depth of lesion of precentral arm area of fig. 1 by thermocoagulation. In series I zones A and B were destroyed, in series II only zone A, that of the outer three cortical layers, was destroyed.

stages of partial paralysis, until in about two or three weeks all symptoms had disappeared.

This is essentially the same clinical picture as after surgical extirpation of the whole precentral arm area, except that the period of total paralysis as well as that of partial paralysis is shorter with the thermocoagulation method. This difference is, in all probability, mainly due to the fact that with the thermocoagulation method part of the cortex of the precentral arm area, about one-fifth of the area on the surface, or one-sixth of the total area, is left behind undamaged on the anterior wall of the central sulcus (see fig. 2).

The limitation of this method of thermocoagulation, at least in its present form, is that only the cortex lying on the surface of the hemisphere can be reached. Several times the attempt was made to include those portions of the cortex hidden in the depth of the larger sulci by opening these up. But, as might have been expected beforehand, without success, because the opening up of these sulci cannot be done without serious injury to the large blood-vessels running along the larger sulci. This obviously results in severe, uncontrolled damage to the cortex supplied by these blood-vessels. Therefore, for the present the method of laminar thermocoagulation can be used satisfactorily only on those portions of the cortex which are readily exposed on the surface of the hemisphere.

The exposed surface of the precentral arm area in the brain represented in fig. 1 (life size) measures with the planimeter 250 square mm. The part of the precentral cortex on the anterior wall of the central sulcus measures about 74 mm.²; of this area about 18 mm.² are destroyed in the case of the thermocoagulation of the outer three layers, and about 27 mm.² if the thermocoagulation involves the whole thickness of the cortex. Thus about 56 mm.² or 47 mm.² of undamaged precentral cortex, hidden in the central sulcus, remains.

Another factor which might also be responsible to some extent for the shorter duration of the symptoms after thermocoagulation, is that this method, although killing the cortex, does not produce any of the complications inevitably accompanying surgical lesions, such as hæmorrhages, retraction of tissue and scar formation in the cortex [6].

In the second experimental series, with thermocoagulation of the outer three layers of the precentral arm area, the striking result is the absence of any of the severe paralytic symptoms of the first series of experiments, and that, if any signs of motor impairment are observable, they are very mild, confined only to a slight clumsiness in the finer movements of the contralateral hand, and disappear within a few hours.

These findings lead to the conclusion that *the severe motor symptoms after destruction of the whole thickness of the motor cortex are due to the destruction of the inner two layers.* If the results of the stimulation experiments after laminar thermocoagulation are taken into consideration, it is not improbable that this conclusion could be narrowed down still further, namely, that the severe motor symptoms after destruction of the whole thickness of the motor cortex are due to the destruction of the (fourth) layer of large and giant pyramidal cells. This, however, is

as yet only a probability, and in the absence of precise data pertaining to this point, restriction to the first given conclusion seems advisable.

In addition to the above positive conclusion still another, complementary to the first one, can be drawn, namely, that the *absence of severe motor symptoms of deficit after destruction of the three outer layers is due to the fact that the inner two cortical layers are left intact.* This tends to show that these inner two layers of the motor cortex can act independently of the outer three layers, and suffice to effect adequate motility.

Corroborating this conclusion is a finding obtained along another line of research. In experiments on action currents of the cortex, which will be published elsewhere, it was found that the "spontaneous" action currents which can be derived from various portions of the cortex, and amongst these from the motor cortex (even in a deeply anesthetized animal), are still present, though modified in a more or less typical way, after laminar thermocoagulation of the outer three layers. This observation shows that the inner layers of the cortex, even under these experimental conditions, are in continuous activity.

This functional independence of the inner two layers of the motor cortex of the outer layers, resulting in apparently normal motor control, becomes the more interesting when one is cognizant of the recent studies of Lorente de Nó on the structure of the cerebral cortex. According to de Nó the cortex of the entorhinal region receives three types of afferent fibres all ending in the outer three layers; the large pyramidal cells of this cortex receive all afferent impulses from the subcortical centres and from other cortical areas through the intermediary of the outer three layers. The corticopetal fibres do not give off any branch before they enter the third layer. Within the third and second layers they give rise to complicated arborizations which establish only scarce contacts with the ascending protoplasmic shafts of the deep pyramidal cells, but very numerous synaptic contacts with the intercalating neurones of these superficial layers, and thus indirectly with the bodies and horizontal dendrites of the large pyramidal cells of the inner layers.

Consequently these large pyramidal cells have only a very limited number of contacts with the afferent fibres themselves; by far the greatest number of their synaptic connections is established through intercalating neurones of the superficial layers. Dr. de Nó, with whom I had the opportunity to discuss the results of my experiments, stated that this structural feature of the regio entorhinalis is true also for the motor cortex.

If one accepts these statements the conclusion would seem to be that the activity of the inner two layers, after destruction of the outer layers, is to a great extent independent of impulses travelling along the afferent fibre systems just mentioned. The question then immediately arises how the activity of these inner two layers is brought about. Rather than to speculate upon this interesting point, which is difficult to answer satisfactorily at present, I prefer to restrict this paper to the experimental facts and to the immediate conclusion which they seem to warrant.

This conclusion is that the experiments reported in this paper, by themselves and in combination with the outcome of the stimulation experiments after thermocoagulation of the outer three layers of the motor cortex reported previously, show that the inner two layers of this cortex can react and act independently of the outer three layers.

The facts upon which this conclusion is based are: (1) In absence of the three outer layers the electrical stimulation of the inner two layers elicits apparently normal motor reactions; (2) the preservation and functional activity of the inner two layers in the unanæsthetized monkey, after destruction of the outer layers, suffices to restore almost immediately apparently normal motility.

SUMMARY.

(1) The destruction by thermocoagulation of the whole thickness of the cortex of the precentral arm area on the surface of one hemisphere in the monkey results in a paralysis of the contralateral arm. This paralysis lasts for a few days, then gradually subsides. After two or three weeks all noticeable motor disturbances have disappeared.

(2) The destruction of the outer three layers of the cortex of this same area results at most in very slight symptoms of motor impairment in the finer movements of the contralateral hand. In some monkeys no symptoms of deficit can be detected at all, in most of the animals they are noticeable. When present, these mild symptoms are always very transient; in some monkeys they can be observed for a few hours only; the longest period through which they could be observed, was seventeen hours. After this variable period all movements are apparently entirely normal.

(3) From these results it is concluded that the severe symptoms of motor impairment following destruction of the whole precentral cortex, either by thermocoagulation or by surgical procedure, are due to the destruction of the inner two layers of this cortex.

(4) The preservation and functional activity of these two layers in the unanæsthetized monkey (*Macacus*) suffices to restore almost immediately apparently normal motility.

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NOTICES OF RECENT PUBLICATIONS.

The Brain and its Mechanism. By Sir CHARLES SHERRINGTON.
The Rede Lecture. Cambridge University Press. 1933. Price
1s. 6d.

In his Rede Lecture, Sir Charles Sherrington has distilled for us a quintessence of his life's work, and it has a fragrance and a delicacy worthy alike of its author and its subject.

Both the neurologist and the psychologist must profit from the careful consideration of what he has to say, for he deals with an incomparable knowledge with that borderland of their respective territories that is so ill defined and so disputed, namely the relation of mind and brain.

With few exceptions, the psychologists have sought to erect a high barrier here as though they could not bear to face the complexities and difficulties of the physiology of "the organ of mind," and were trying vainly to hide from them. On the other hand, the neurologist will not readily admit that any frontier should exist, but he shrinks from a bold advance into the tangled undergrowth of verbiage in which the modern psychologist spins so profusely his intricate webs of speculation. It is not possible here to summarize what is already a summing up by a master, but the neurologist will take courage from the modest but courageous approach which Sir Charles Sherrington here makes to the subject.

Œuvre scientifique. Recueil des principaux travaux de J. Babinski.
Paris: Masson et Cie. 1934. Pp. 633. Price 180 francs.

The neurologist will welcome this collection of the long and fruitful labours of this French master of clinical neurology. Of their scientific value it is unnecessary at this time to speak, but in addition to their content the reader will delight in the lucidity and economy of these writings.

Of particular historical interest is the little paper in which Babinski first reported that "phénomène des orteils" which has made his name an integral part of neurological terminology. Many less significant discoveries have, and are still being, presented to the neurological world at much greater length.

The wide range of Babinski's labours may come as a surprise to those of a younger generation. The nosography of every aspect of disease of the nervous system, treatment and pathology are all nobly represented, as well as notable contributions to the study of hysteria.

The volume is assured of a warm welcome wherever neurology is studied.

Illustrations of Regional Anatomy. Section I.—Central Nervous System.

By E. B. JAMESON. Edinburgh: E. & S. Livingstone. 1934.
48 Plates. Price 7s.

The author says in a preface that the plates here reproduced are "paraphrases of the blackboard diagrams that have illustrated his lectures." To his old students they will recall delightful hours in the anatomy class at Edinburgh, and to all they have the value inherent in beautiful and exact drawings. The plates are collected in a loose leaf cover, so that they can be used in whatever order the worker prefers. Another welcome innovation is that the arteries and veins of the brain are fully illustrated, not only on the surface but even in the cut sections. The diagrams of horizontal sections of the brain-stem and cord and of the motor and sensory paths are perhaps less successful. The neurologist would like a series of plates, at least as numerous as those dealing with the macroscopic anatomy, to illustrate the nuclei and fibre systems of the central nervous system, but these needs are not shared by the undergraduate for whom the atlas is prepared.

Chirurgische Neuropathologie. Bd. ii. Das Rückenmark. von L.

PUUSEPP. Tartu (Dorpat): J. G. Krüger. 1933. S. 679.
Price £2.

The second volume of Professor Puusepp's treatise on the surgical neuropathology of the nervous system is devoted to the vertebral column and the spinal cord. Though it is written from a surgical angle it is really a comprehensive textbook on diseases of these parts, for it deals in detail with many conditions which scarcely lie within the sphere of operative intervention or of other surgical activity. The plan of the book suggests that it is intended for surgeons who have had little experience or training in neurology, for the first 60 pages are concerned with the minute anatomy and the physiology of the cord; the second section deals with the pathology of the cord and its membranes, and is followed by a third section of over 70 pages on the physiology and pathology of the cerebrospinal fluid. These sections are admirably written and though the reader may be unable to accept many statements or hypotheses presented in them they are worthy of every student's attention. In perusing them, however, the question constantly arises as to whether these fundamental subjects would not be better dealt with in separate monographs. The next chapters on the symptomatology and localization of spinal lesions is much shorter, and is in many respects disappointing. That on operative technique occupies less than 30 of the nearly 700 pages in the book, but it is sound and reliable.

The most interesting and valuable pages are the 200 in which diseases and injuries of the vertebral column are described. The clinical and the pathological features of its commoner affections and injuries, as well as rarer forms of spondylitis, are treated in such detail from the author's own experience and

a survey of the literature that it is difficult to recall any monograph to which the student of these conditions could be more safely referred. The following sections are devoted to traumatic lesions of the cord, disease of its membranes, intra- and extra-medullary tumours and syringomyelia. The author, who claims to have originated the surgery of the latter disease, is a warm advocate of its operative treatment; it is apparently unknown to him that more than thirty years ago Horsley practised systematically what he now recommends.

This volume bears the stamp of its author's extensive experience and skill, and can be strongly recommended to a wider circle of readers than it is primarily intended for. It is copiously illustrated and is provided with an excellent index.

Kompndium der topischen Gehirn-und Rückenmarksdiagnostik. Von
R. BING. Berlin: Urban und Schwarzenberg. 9te. Aufl. S. 266.
Price Rm. 9.

Since this Compendium was last noticed in this Journal, two new editions have appeared, the present being the ninth. Without notably increasing its size, the author has sought to keep the book abreast of modern knowledge.

As expressly stated in the introduction, the book is based upon the applied anatomy and physiology of the nervous system, and it probably owes its justly considerable popularity to the accuracy and lucidity of its anatomical sections. In respect of these, it remains the best available work of its kind.

It may be questioned, however, whether modern neurophysiology has ever been quite successfully embodied in the Compendium, for it is not enough to add short references to new views, if the old are not correspondingly modified or, if necessary, abandoned. It is particularly to the matter dealing with the reflex phenomena in spinal cord lesions that these criticisms may be said to apply most nearly. The account of these is lacking in clarity; the flexed and extended types of spastic paraplegia are not described nor the factors underlying their appearance discussed. Indeed, they find a bare mention under the misleading titles of "tendino-reflex" and "cutaneo-reflex" paraplegia. No mention is made of inversion of the radial reflex (Babinski) in lesions involving the fifth cervical segment, and this inversion is wrongly described (p. 33) as characteristic of pyramidal lesions.

The section on cerebellar functions includes a statement that the spino-cerebellar pathway conveys impulses underlying "deep sensibility" to the cerebellum, and the whole section takes little account of the advances of the past twenty-five years.

That nine editions of the Compendium have been called for since its first appearance in 1909 indicates its usefulness and popularity, and if it were brought thoroughly up to date in its physiological sections its author might confidently look for another quarter century's life for it.

Unfall und Hirngeschwulst. VON O. MARBURG. Wien: Julius Springer. 1934. S. 106. Price Rm. 8.80.

In this interesting and well-documented monograph, the author has collected from the literature a large number of cases of intracranial tumour in which a history of head trauma was obtained. He also includes an exhaustive clinical and pathological report on three personally observed cases.

There is a reasoned discussion of the evidence and the author comes to the conclusion that head injury must be accepted as a not uncommon factor in the production of intracranial tumours.

A study of the monograph is essential to all interested in this difficult problem.

Les Tumeurs de la Loge cérébraleuse. Par Th. de MARTEL et J. GUILLAUME. Paris: G. Doin et Cie. 1934. P. 454. Price 90 fr.

The chief interest of this monograph is that it is written from the personal experience of two well-known surgeons. The first 180 pages are devoted to the symptomatology and the differential diagnosis of tumours of the posterior fossa of the skull, a long chapter on surgical technique follows and the rest contains the clinical and post-mortem records of 55 selected cases. The descriptions of the symptoms produced by these tumours, and especially of those resulting from cerebellar lesions, add little to what is contained in most textbooks and is familiar to practising neurologists. A more direct and simple statement of their own clinical experiences would have been more instructive than the lengthy reviews they give of the opinions of others, but these chapters are certainly not without value. They propose no revolutionary innovations in operative methods, and their results seem to justify those which they adopt.

Physiology of the Central Nervous System and Special Senses. By N. J. VAZIFDAR. Bombay: Ideal Books Co., London: H. K. Lewis. 1934. Sixth Edition. Pp. 341. Price 10s. 6d.

From a modest beginning this book has grown in successive editions to a large textbook, perhaps too large for its purpose. It is admittedly only a compilation intended for students and it naturally shows the defects that a volume written from such sources rather than from personal knowledge must inevitably have, but as it presents information in a concise and easily studied form it will prove useful to those preparing for qualifying and post-graduate examinations. In several chapters information is summarized in tables and illustrated by simple diagrams which facilitate study. Some of the fundamental work on nervous physiology is neglected and many statements in it cannot pass question, especially when the author refers to the clinical applications of

physiological facts and when he attempts to explain more than the present state of our knowledge justifies. But on the whole the book, which is well written, can be safely recommended to those entering on the study of the nervous system.

Craniocerebrale Schemata für die Röntgenographische Lokalisation.
VON A. SCHÜLLER und H. URBAN. Leipzig und Wien: F.
Deuticke. 1934. Price 4 Rm.

The object of the authors of this small brochure, a well-known radiologist and a neurologist, is to facilitate the localization of cerebral lesions visible by X-rays, and the accurate determination of the topographical relation to the brain of injuries and other affections of the skull. For this purpose they provide drawings of a series of sections of the head in which the more important structures of the brain are indicated, and diagrams of surfaces of the brain contained within the skull. The orienting line they adopt passes through the upper margins of the orbit and of the external auditory meatus.

The Patient and the Weather. By W. F. PETERSEN. Ann Arbor:
Edwards Bros. 1934. Pp. 375. Price 5 dollars.

No line of approach to knowledge can be neglected, and important acquisitions have often come from unexpected and over-overlooked sources, but of anyone employing these it may be demanded that his facts are accurately determined and that his reasoning does not pass beyond what the facts warrant. This volume contains a large collection of observations, but many of the conclusions drawn from them will require critical reconsideration, and the author's thesis is unfortunately marred by much uncritical theorizing and by the use of vague and indefinite terms; he speaks, for instance, of the inhabitants of certain American States as "autonomically unstable individuals," assumes that in others "the protoplasmic mass is more stable," and describes the autonomic system as a "cosmic resonator."

Although this is the first to appear, it is to be the third of a series of volumes, the first of which will deal with the response of normal individuals to the meteorological environment, and the second with the effects of meteorological changes on unstable persons. Here the author deals with the influence of weather and other environmental factors on mental and nervous disease. He has thrown his net so wide that it is not possible to refer in a short review to all its contents. Most of the observations were made on patients in a large psychiatric hospital.

His main thesis is that there are two physiological phases which are partly at least dependent on weather; in the one which he labels "A.R.S.," anabolism, alkalinity, vascular spasm and a noxæmia predominate; the other, "C.O.D.," is characterized by catabolism, oxidation, and dilatation of blood-vessels. He produces statistics to show the increase of certain psychoses in some months of

the year, and points out that there may be seasonal variations in others, as in the manic-depressive forms.

Many psychical alterations are, he assumes, actually initiated by meteorological events and he even goes so far as to suggest that these may play a part in embryonic life. Weather may also influence the occurrence or symptoms of organic neurological disorders, as tabes dorsalis and disseminated sclerosis, while poliomyelitis is due to invasion by a virus of tissues in which vascular spasm determined by weather has produced an area of anoxæmia.

The book contains a large number of meteorological charts and other illustrations. In order to reduce the cost of production litho printing has been employed.

La Ponction cisternale (ponction sous-occipitale). Par MARIANO R. CASTEX and LUIS E. ONTANEDA. Paris: G. Doin and Cie. 1934. Pp. 70. Price 35 fr.

This little monograph from Buenos Aires serves a useful purpose in bringing to our knowledge a method of performing cisternal puncture which the authors have devised and used in over 2,000 cases. This depends on exact measurement of the depth of the dura mater from the skin calculated from the distance in a sagittal plane from the point of entry of the needle to the anterior border of the tip of the mastoid processes. From this distance 2 cm. are deducted in the male and 1.7 in the female. The only extra apparatus required for this technique is a small metal square graduated in millimetres. The authors claim that this method almost completely eliminates the risk of pricking the cord or the larger vessels round it. There is also a full description of the anatomy of the suboccipital region, illustrated by excellent drawings. The later chapters on the uses of cisternal puncture and the physiology of the cerebrospinal fluid add little to our knowledge.

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